HIGH SENSITIVITY C – REACTIVE PROTEIN IN ACUTE ISCHEMIC STROKE

submitted to
The Tamil Nadu Dr.M.G.R. Medical University

M.D. DEGREE EXAMINATION
BRANCH – I (GENERAL MEDICINE)

Dr.R.Sivaraman

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI

April 2016

BONAFIDE CERTIFICATE

This is to certify that **"STUDY ON HIGH SENSITIVE C-REACTIVE PROTEIN OF ACUTE ISCHEMIC STROKE"** is bonafide work done by **Dr. R. SIVARAMAN,** post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of **The Tamilnadu Dr.M.G.R. Medical University** for the award of **M.D. Degree Branch I (General Medicine)** during the academic period from JULY 2013 to JUNE 2016.

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ACKNOWLEDGMENT CERTIFICATE FROM GUIDE

I Dr. C. Hariharan, Professor of medicine, Govt. Kilpauk medical college hospital, the guide for this study "Hs-CRP in acute ischemic stroke" done by Dr. R. Sivaraman, M.D General medicine, solemnly affirm that the above study is done abiding to rules and regulations as adviced by the Ethical committee.

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DECLARATION CERTIFICATE

I hereby certify that i am the sole author of this **STUDY ON Hs-CRP IN ACUTE ISCHEMIC STRO**KE done at Kilpauk Medical College. I certify that this is the true copy my thesis,including any final revisions, as approved by my ethical committee done under the guidance of **Dr.C.Hariharan MD , Professor of Medicine.**

Date:

Place:

(Dr.R.Sivaraman)

Signature and name of the candidate

ETHICAL COMMITTEE OF
GOVERNMENT KILPAUK MEDICAL COLLEGE HOSPITAL
KILPAUK, CHENNAI-10.
Venue: Dean Chamber, Date: 15.6.2014

Chair person
Prof. Dr.N.NARAYANABABU, M.D,

The Dean
Govt. Kilpauk Medical College & Hospital,
Chennai - 600010.

TO WHOMSOEVER IT MAY CONCERN

Dear Sir / Madam

Sub: Internal Medicine – MD PG's Dissertation Ethical Committee – Reg.

Ref: Requisition from H.O.D. Medicine.

This is in reference to the letter dated 2.1.20 regarding Ethical committee meeting clearance with regard to the following topics

s.no	Name	Topic
1	Dr.R.Sivaraman	A study on Hs-Crp in acute Ischemic stroke
2	Dr. S. Karthikeyan	Thyroid dysfunction in Metabolic syndrome
3	Dr.Dilip	TIMI score in ST elevation MI and its correlation with single quantitative troponin T and EF< 40%
4	Dr. Umalakshmi premnath	Microalbiminuria in non –diabetic acute ischemic stoke –prevelance and severity

5	Dr. Ibrahim sameem kahn	A study on clinical profile of Leptospirosiswith its spcial reference to multiorgan involvement
6.	Dr. Jeevitha Rajalakshmi	A study of carotid intima media thicknessas a predictor of macrovascular complication in type 2 DM
7	Dr.A.Balamurugan	A study of clinical,radiological,bacteriological pattern of PTB among HIV seropositive patients
8	Dr.S.Saranya	Dyslipidemia in subclinical hypothyroidism
9.	Dr. Sivanesan	Functional independence score in people with haemophilia and factors affecting it
10	Dr.Settu selvaraj	Clinical and histopathological profile in patients underwent renal biopsy in tertiary care centre
11	Dr.Kiruthika	To correlate the relation between insulin resistance and serum triglycerides in euglycemic cirrhotics
12	Dr. Ramesh	Study on EECP in CAD patients with low EF
13	Dr.Swetha sattanathan	A study on the effect of microcytic anemia on HBA1c levels in non diabetic individuals
14	Dr.Manikandan	A study on platelet volume indices in acute coronary syndrome
15	Dr.Manian	A study on pleural fluid cholesterol and lactate dehydrogenaseto differentiate exudate and transudateand comparing it with Light's criteria
16	Dr. Kiran josy kanjamala	Hyperhomocystenemia in acute ischemic stroke

We confirm that no member of the study team is on the Ethics Committee and no member of the study team voted.

The trial will also follow the Ethics Guidelines for Bio-Medical Research on Human subjects issued by ICMR, New Delhi and will not involve any expense to the Government and will not be detrimental to the normal functioning of the Institution.

The study will also satisfy the revised order issued by the Government of Tamil Nadu, Health and Family Welfare Department G.O.MS.No:319, H & FW, Dept. dated 30.11.2001.

ACKNOWLEDGEMENT

I sincerely thank **Prof.R.NARAYANBABU, M.D.,** Dean, Kilpauk Medical College, Chennai for permitting me to utilize the facilities needed for this dissertation work.

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I owe my sincere gratitude to my Chief **Prof. C.HARIHARAN,M.D.,** Professor of Medicine, Kilpauk Medical College for his esteemed guidance and valuable suggestions in all the stages of this dissertation.

I also express my sincere gratitude to **Prof.T.RAVINDRAN M.D., Prof.C.KULOTHUNGAN,M.D., Prof.S.SURENDRAN,M.D.,** for their help and guidance rendered during the entire period of my work.

I whole heartedly express my sincere thanks to **Prof. S.ARUNAN,** M.D(Gen Medicine), DM (Neurology), Professor of Neurology, Kilpauk Medical College, Chennai for his valuable guidance throughout my dissertation work.

I whole heartedly express my sincere thanks to **Prof. S.RADHIKHA M.D.,** Professor and Head, Department of Biochemistry, Kilpauk Medical College, Chennai for her valuable guidance and also for allowing

me to use the Biochemistry Laboratory for the measurement of High Sensitivity C – Reactive Protein.

I wish to thank **Dr.D.venkteswarlu MD**, Registrar, **Dr.Malarvizhi M.D., Dr. Shridharan, M.D.,** Assistant Professors, Department of Medicine, Kilpauk Medical College for their valuable suggestions and help rendered throughout this work. I also thanks **Dr. Murugapandian, M.D.,** DM, Assistant Professor Department of Neurology, Kilpauk Medical College, for his valuable guidance and support throughout my dissertation work.

I also extend my thanks to all the laboratory technicians in the Biochemistry Department for their valuable support throughout my dissertation work.

I also thank my parents, my spouse, colleagues, friends and staff of our hospital, for their support for this work.

Last but not the least, with sincere gratitude, I thank all the patients who contributed so much to this study without whom this study could not have been possible.

CONTENTS

INTRODUCTION

INTRODUCTION

In recent years, there has been increasing evidence which shows strong links between inflammation and the pathogenesis of atherothrombotic stroke. Acute phase proteins have been implicated to play roles both during acute and chronic inflammatory processes in different diseases including ischemic stroke. Even low grade infections may cause elevation of various acute phase reactants which may partly be responsible for the inflammatory process observed in atherosclerotic lesions, which may inturn relate to occurrence of ischemic symptoms.

Inflammation plays a major role in atherothrombosis and measurement of inflammatory markers such as C–Reactive Protein, an acute phase reactant that reflects low-grade systemic inflammation has been studied in a variety of cardiovascular diseases. There is growing evidence of the prognostic importance of CRP in ischemic stroke. Also CRP has been found to be a strong but relatively non-specific risk factor of fatal stroke in elderly persons.

CRP, a sensitive meter of inflammation, induces vascular thrombosis by stimulating monocytes to express tissue factor, the initiator of the extrinsic pathway of coagulation. Elevated levels of CRP are found to be related with higher risk of first-ever cardiovascular, cerebrovascular and peripheral vascular diseases.

The WHO has recently set international reference standard for the use of highly sensitive CRP assays. This has enhanced the usefulness of CRP as a reliable predictor of cardiovascular events.

AIMS AND OBJECTIVES

AIM

1. To evaluate the predictive value of hs-CRP in relation to first ever ischemic stroke.

2. To correlate the hs-CRP levels with various cardiovascular risk factors.

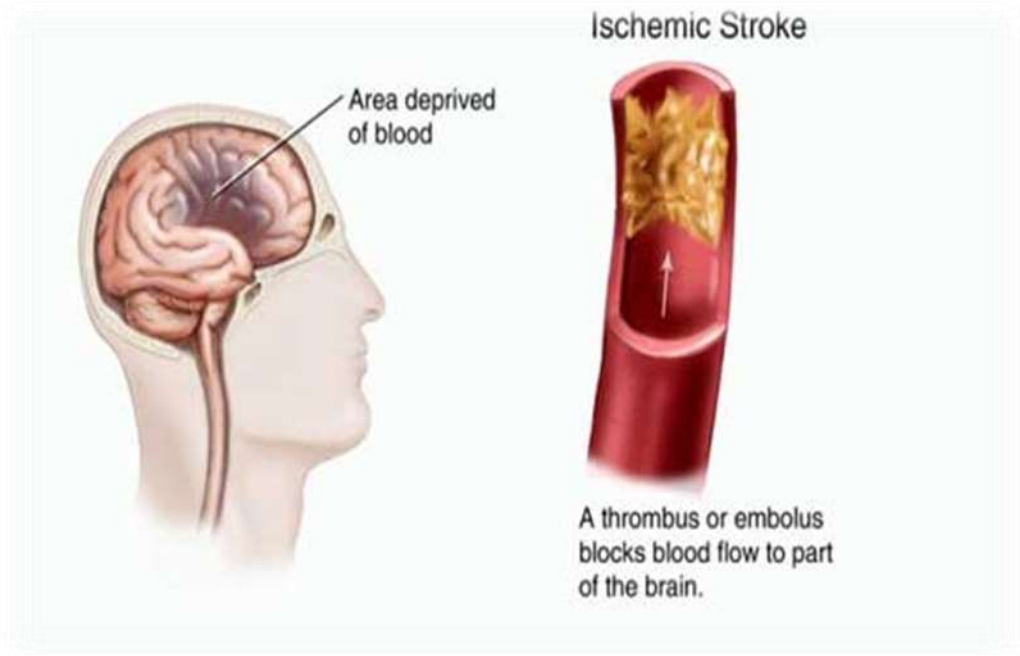
REVIEW OF LITERATURE

REVIEW OF LITERATURE

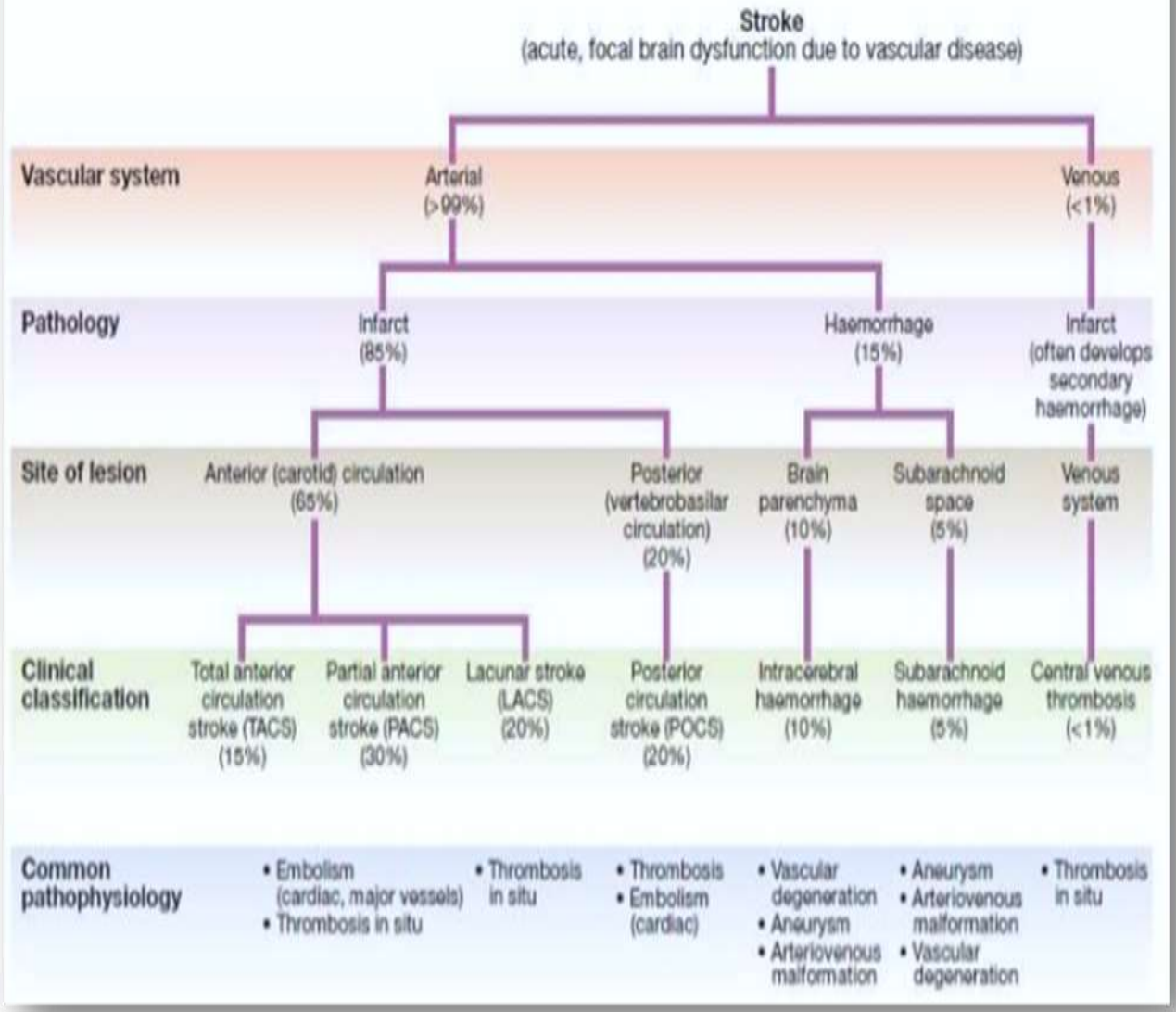
CEREBROVASCULAR ACCIDENT / STROKE:

Cerebrovascular accident or stroke occurs due to sudden death of brain cells in a localised area of the brain due to inadequate or lack of blood flow.

Depending on the area affected it can cause loss of memory, loss of speech, inability to move limbs, coma or even death.



Classification of Stroke



CAUSES OF CEREBRAL ISCHEMIA AND INFARCTION

- Congenital arterial anomalies
- Dissection
- Atherthromboembolism
- Intracranial small vessel disease (lipohyalinosis, microatheroma)
- Arterial Wall disorder
- Trauma
- Inflammatory vascular disease
- Embolism from the heart
- Irradiation, infection
- Moya Moya syndrome
- Binswanger disease
- Embolism from arterial aneurysm
- Hematological disorders
- Fibromuscular dysplasia
- Paradoxical emboli
- Miscellaneous:

  Migraine

  Pregnancy

Cancer

Drug Abuse

OCP

Homocystinemia

IBD

Fabry's disease

Mitochondrial Cytopathy

Hypoglycemia

Hypercalcemia

Fat embolism

Epidermal nevus syndrome

Acute leukemia's

SLE

Anti thrombin III deficiency

Protein C Defeciency

Protein S deficiency

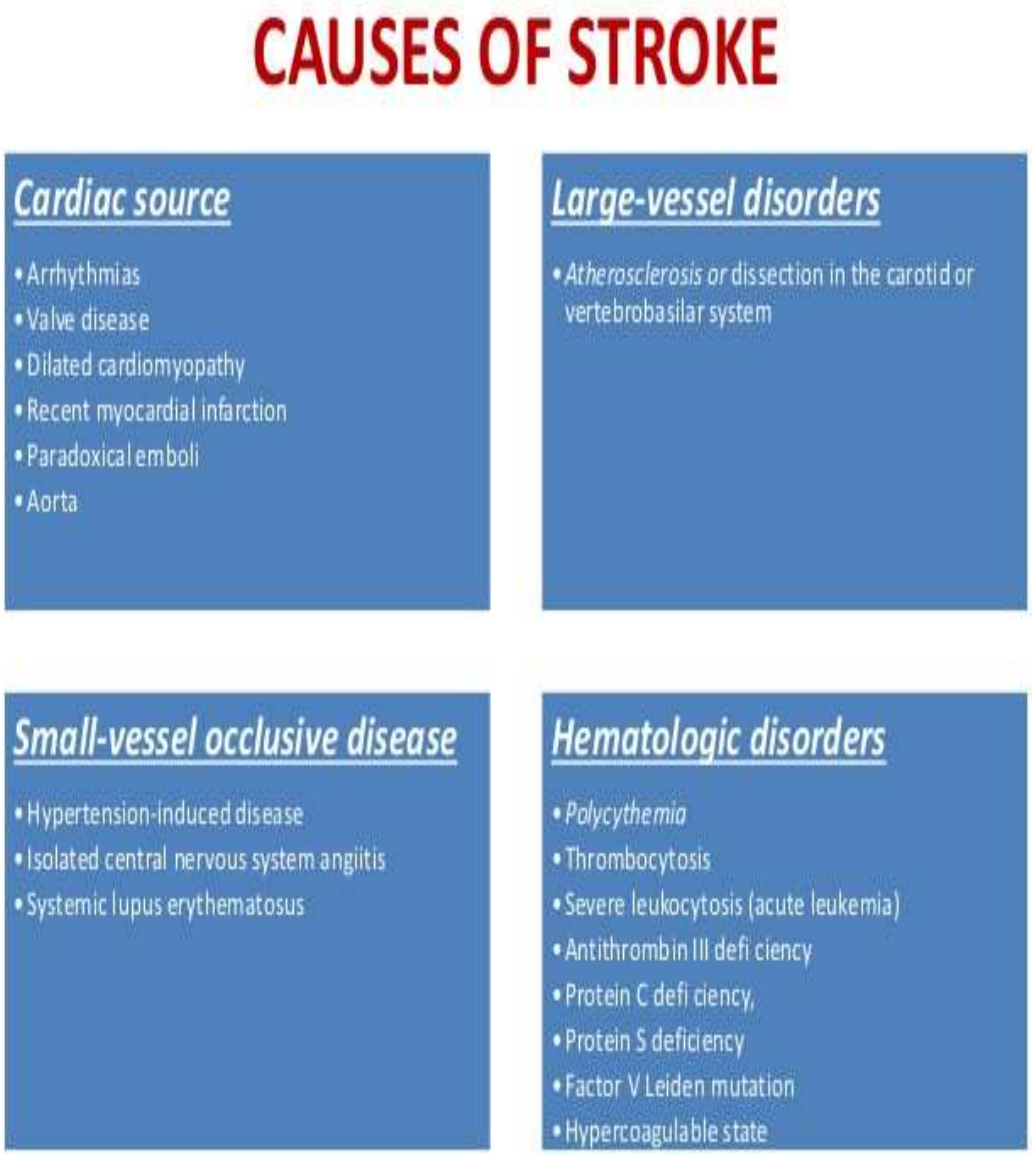
Factor V leiden Mutation

Hypercoagulable states

Thus it is evident that:

- 50% cases of CVA is due to athero embolism of cerebral artery

- 80% CVA is due to cerebral infarction



STROKE IN YOUNG

Occurs in < 40 yrs of age

Causes:

I. Infants and children –

- CAHD
- AVM
- Thrombosis of veins

II. Children and Young adults-

1. CVS –

- RHD
- IE
- Embolism
- Prosthetic valve
- MVP
- Left atrial myxoma

2. Arteritis –

- TB
- Syphilis

- Takayasu’s arteritis
- aortoarteritis

3. Collage vascular disease-

- SLE
- APLAS
- Rheumatoid arthritis
- Mayo-mayo’s disease

4. Inborn errors of metabolism

- Homocystinuria
- Allopunuria

5. Haematological causes

- Sickle cell disease
- G6PD deficiency

6. Congenital causes-

- factor 12 deficiency
- high concentration of factor 8
- hyperfibrinogenaemia
- heparin co factor II defeciency
- hyperhomocyteinemia

ATHEROSCLEROSIS

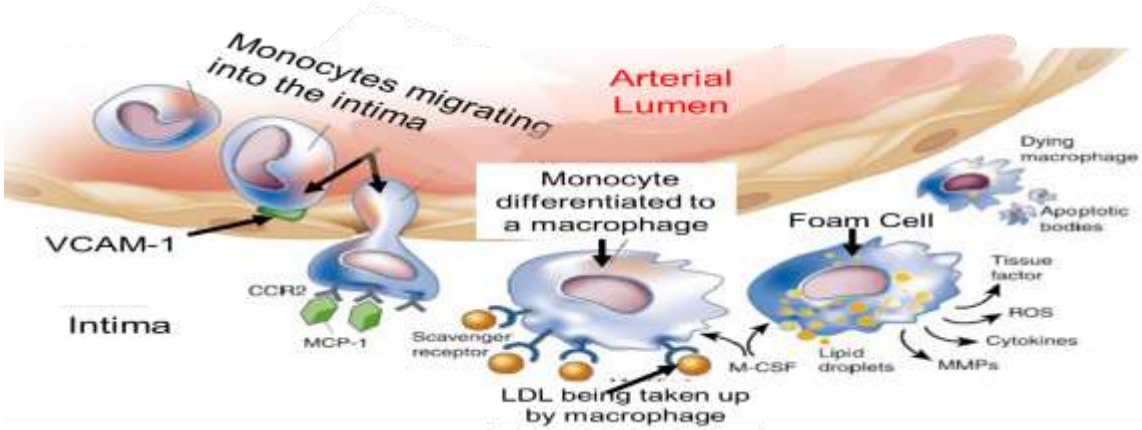
Atherosclerosis remains the major cause of death and premature disability in the developed society. It affects various regions of circulation preferentially, and presents with distinct clinical picture, i.e, MI due to atherosclerosis of coronary blood vessel, atherosclerosis of blood vessels supplying the brain cause TIA & Stroke, in peripheral circulation it causes intermittent claudication, gangrene, it can also produce renal artery stenosis.

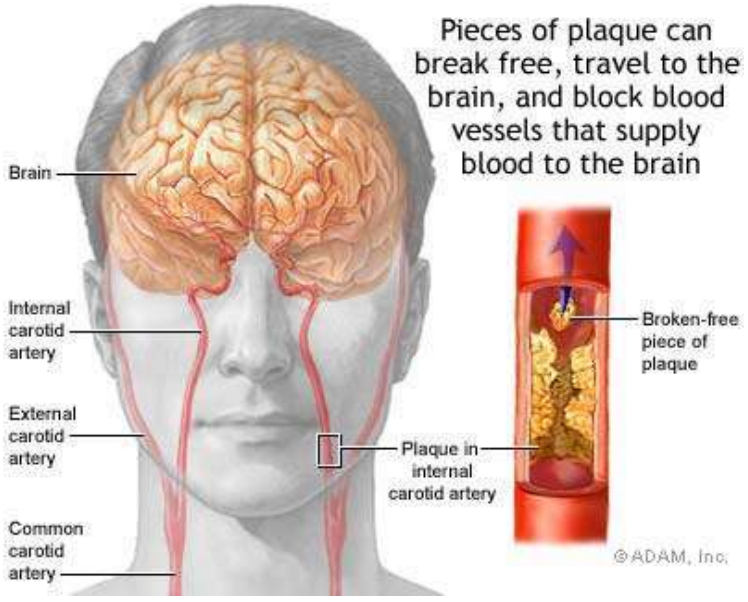
There is accumulation of lipoproteins within the initmal layers of blood vessel and then bind to matrix macromolecules and undergoes oxidative damage, furthermore leads on to production of inflammatory cells within the plaque. Inflammatory cells like monocyte derived macrophages and lymphocytes along with various cell adhesion molecules accumulate at the site of plaque. Macrophages evolve into foam cell rich in lipid then leading on to the formation of fatty streak (precursor of fully formed athermatous plaque)

Adipose tissue derived macrophages may be the primary source of many proinflammatory cytokines, like - CRP, IL -1 , 6 , 8 ; resistin , TNF – alpha.

CRP has been used to understand the inflammatory components of atherosclerosis than other inflammatory mediators such as IL-6 & TNF –

alpha. CRP has been researched over a decade in the role of atherosclerotic diseases. Its assessment can give an approach towards prognosis in ACS & CVA patients especially in first ever stroke.





RISK FACTORS FOR STROKE

Since stroke is a multifactorial disease, both environmental and and genetic risks affect the disease.

1. Age and gender

Stroke incidence increases with age. Risk doubles with each decade after 55 years. Approximately 80% of strokes occur in elderly persons.Sex of the person also affects the risks. Men develop strokes at a higher rate than women up to age of 75.

2. Smoking:

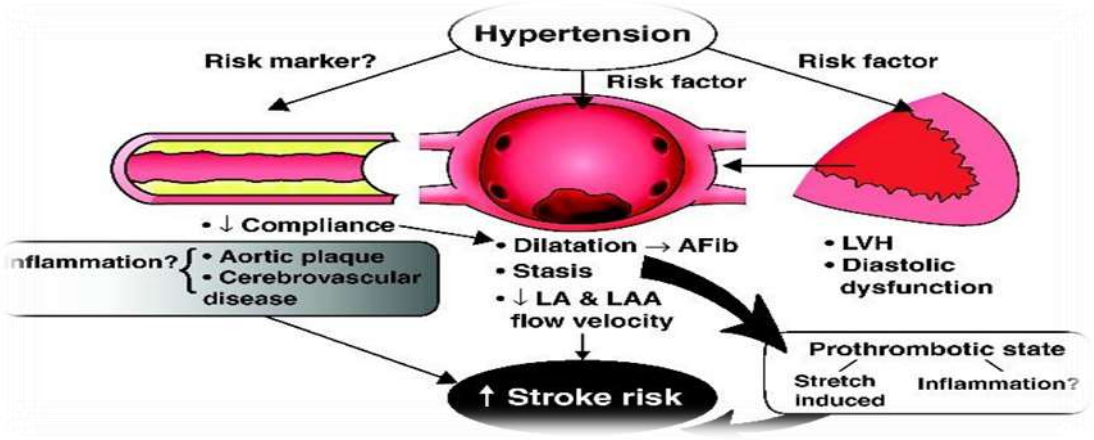
Smoking is a well established risk factor for stroke. A meta-analysis has shown a 50% increase in stroke risk among the smokers.

3. Diabetes Mellitus:

Diabetes increases stroke risk to 2 to four fold compared to non-diabetes subjects and also increasing mortality and morbidity after stroke.

4. Hypertension:

High blood pressure damages the entire arterial tree, it's a modifiable risk factor in acute CVA / ACS .



5. Hypercholestrolemia:

Both elevated LDL as well as serum cholesterol increases the risk of stroke and CHD.

6. Homocysteinemia:

Hyperhomocysteinemia has been described as a possible risk factor for ischemic stroke. Presumed mechanism is raised stress tolerance of the endothelium, inflammation,thrombosis, and oxidative stress.

7. Inflammation and bio-markers:

Inflammation as part of atherosclerotic pathway has been implicated in ischemic stroke and cardiovascular disease. Inflammatory

biomarkers such as HSP, IL-6 and CRP have been shown to be increased in acute ischemic stroke.

8. Evidence of existing vascular disease:

Myocardial infarction

Cardiac failure

Peripheral vascular disease

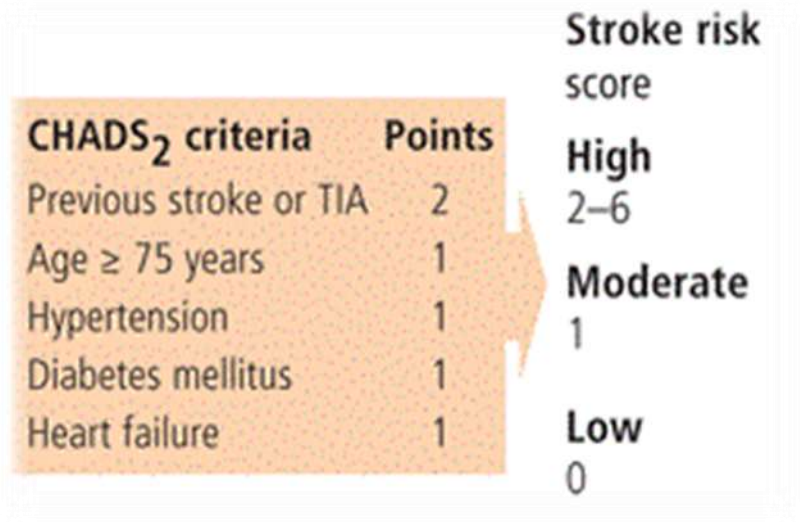
Atrial fibrillation

Carotid arterial bruit and stenosis

Transient ischemic attacks

9. Miscellaneous:

Plasma fibrinogen, Alcohol, OCP



$CHADS_2$ criteria	Points
Previous stroke or TIA	2
Age ≥ 75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Stroke risk score

High
2–6

Moderate
1

Low
0

PREDICTORS OF STROKE OUTCOME

I) Demographic factors:

1. Age:

Age is one of the major risk factors that negatively influence the outcome of patients with ischemic stroke. Recovery of elderly patients is less likely when compared to younger patients.

2. Gender:

Few studies have shown men are associated with poor outcome whereas few other studies have shown no difference in predisposition. The explanation for this might be hormonal. Oestrogen seems to be an important mediator of outcome after ischemic brain injury.

3. Race/Ethnicity:

There is no significant difference in the outcome of incidence of stroke among different races & ethinicity

II) Cerebrovascular risk factors:

1. Previous stroke and atrial fibrillation:

Patients with previous history of stroke and atrial fibrillation are associated with more severe, disabling and higher moratlity.

III) Clinical findings:

1. Level of consciousness and gaze deviation:

Level of consciousness is an important predictor . The presence of gaze deviation & decreased level of consciousness predicts poor outcome.

2. Blood Pressure:

Abnormal blood pressure may influence outcome. High BP have negative long term effect on BBB function. And , so, decreased BP has shown decrease in blood flow in the infracted area.

3. Temperature:

For each one degree celsius rise in body temperature, the relative risk of poor outcome increases twice . This is due to increased concentration of excitotoxic neurotransmitters . Higher temperature (>37.5^{0}C) is an important predictor of large volume infarct and higher neurological deficit when it occurred in the first day after stroke onset.

IV) Laboratory findings:

1. Glycine and glutamate:

Raised glycine or glutamate levels strongly correlate with large infarct size and disabling neurological deficits.

2. S-100:

Elevated serum levels of S-100 correlate with poor neurologic outcome.

3. Neuron-specific enolase:

This enzyme has been shown to rise in acute stroke.

4. Serum Glucose:

Elevated blood glucose is associated with increased mortality and morbidity. Elevated blood glucose seems to produce its negative effects by causing a profound cellular acidosis. Clinical studies have shown an correlation between elevated blood glucose and cerebral oedema.

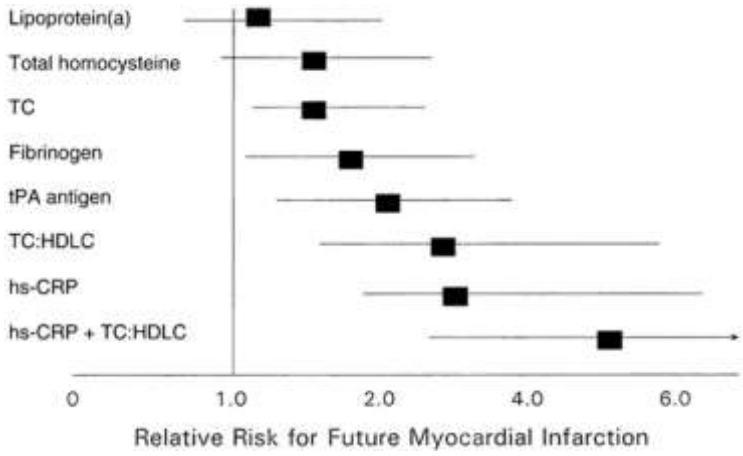
PROGNOSTIC VALUE OF ACUTE PHASE REACTANTS (APR)

1. Erythrocyte Sedimentation rate (ESR):

Raised ESR predicts poor outcome.

2. C-reactive protein (CRP):

CRP concentrations measured within 3 days of stroke individually predicted survival after ischemic stroke. Patients with levels above 10.1 mg/L had significantly poor survival rate.

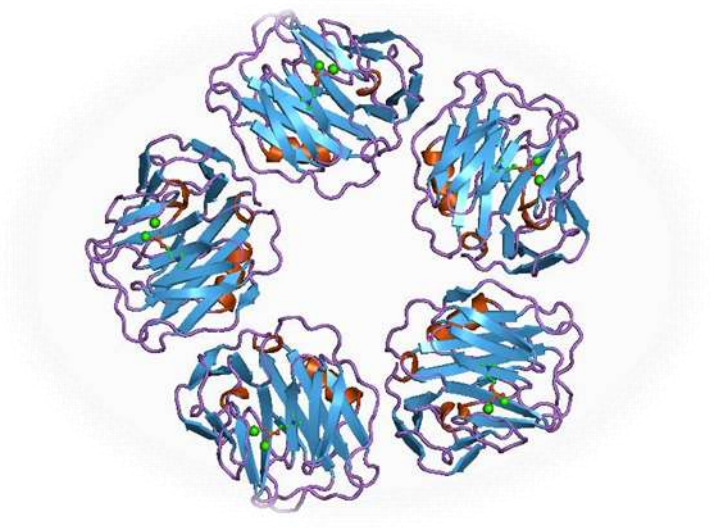


C REACTIVE PROTEIN

History and nomenclature:

CRP founded in 1930 by William S Tillet and Thomas Francis is a petameric protein detected in the serum of patients with acute inflammation.

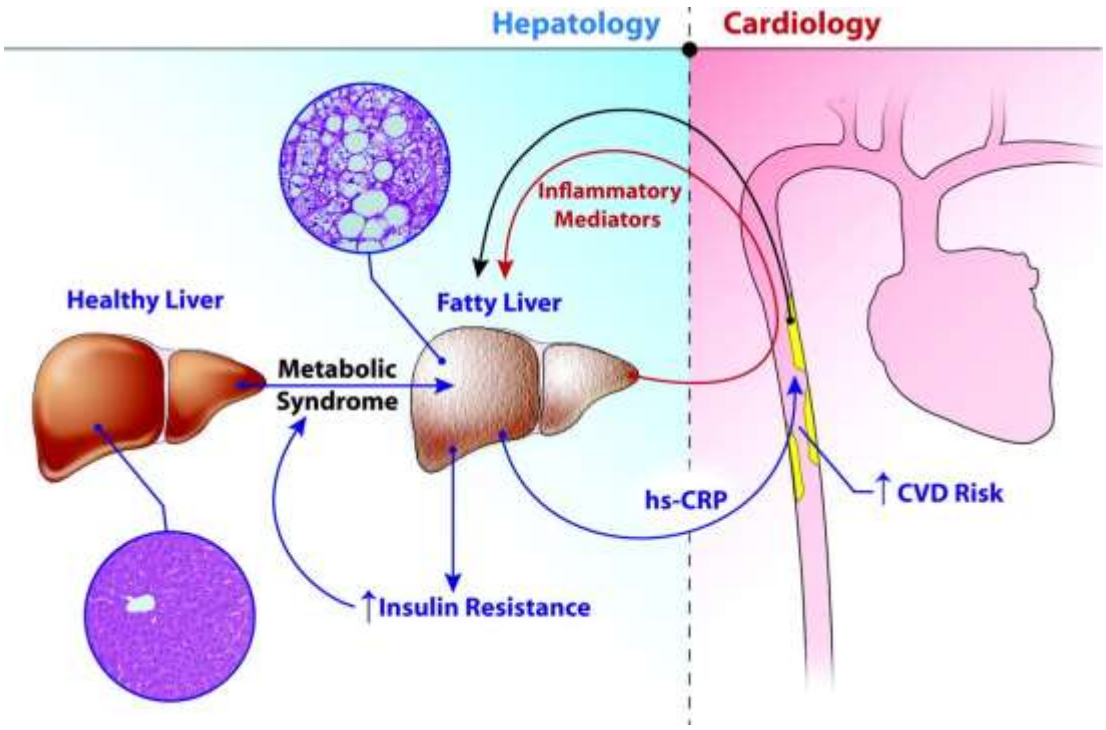
Genetics and Biochemistry:



The gene for CRP is located in 1q21-q23 , its an residue protein with molecular mass 25106Da. C stands for carbohydrate to which it bind to capsule of pneumococci.

FUNCTION OF CRP

It's a major component of acute phase proteins. It is generated in liver and is present in circulation in very low concentration (<1mg/dl). It is involved in activation of immune system through complement cascade.



DIAGNOSTIC USE

Estimation if CRP is important in evaluation on acute phase response, which useful to determine the disease process and success of the treatment. If the recovery is complicated by any infection it will be reflected by continuous elevation of its level which needs further intervention.

CRP IN ATHEROSCLEROSIS

CRP has been used to understand the inflammatory components of atherosclerosis than other inflammatory mediators such as IL-6 & TNF – alpha. CRP has been researched over a decade in the role of atherosclerotic diseases. Its assessment can give an approach towards prognosis in ACS & CVA patients especially in first ever stroke.

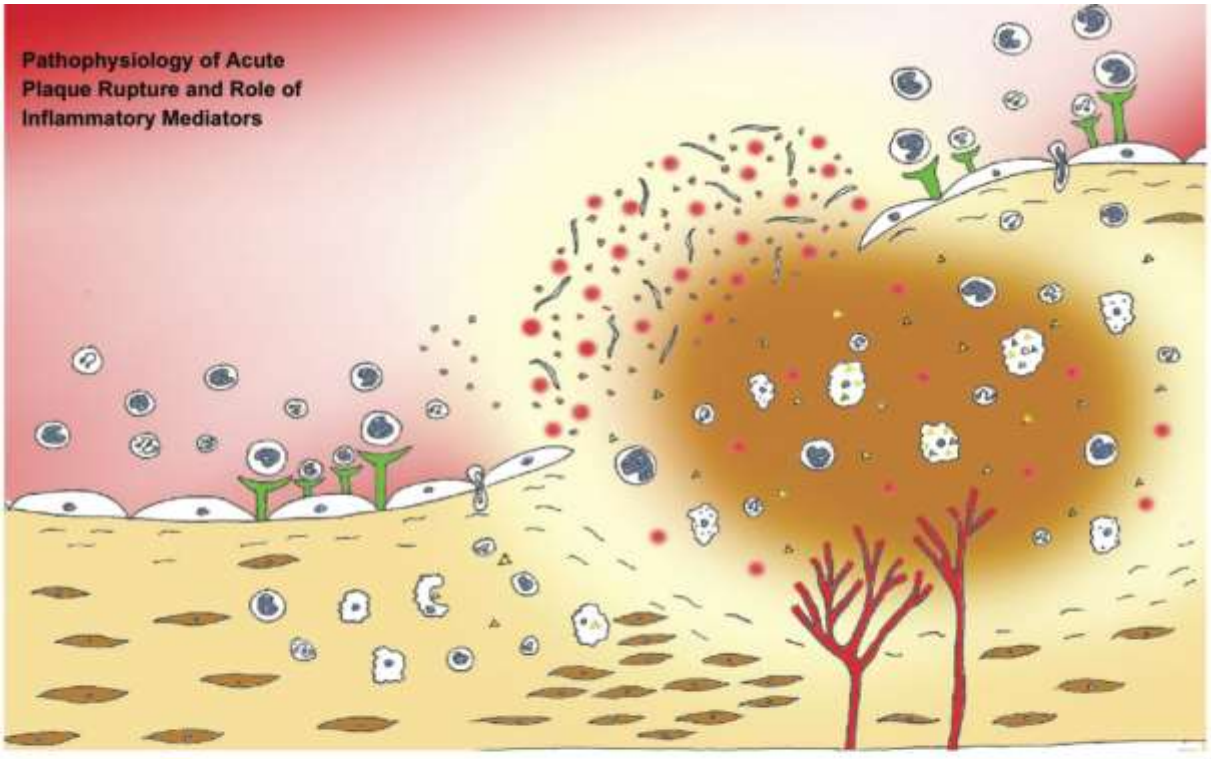


FIGURE 1. Ruptured plaque: transmigration of white blood cells (WBCs) is promoted by selectins and inhibited by IL-10. MCP-1) promotes the attraction and activation of WBCs to sites of inflammation. These bind to adhesion molecules that are promoted by IFN-γ prior to transmigration across the endothelium. Once within the tunica media, the inflammatory cells are stimulated by MPO and IL-6 to phagocytose cholesterol crystals. Lp-PLA2 is released by inflammatory cells within the atherosclerortic plaque to oxidize cholesterol crystals and promote phagocytosis. Angiogenesis into the plaque is promoted by cd40 and HGF. MMPs act on the collagen cap of the plaque to make it unstable and lead to eventual rupture. PAPP-A that is released from unstable plaque downregulates the inflammatory process by releasing IGF-1 into the circulation.

DYNAMICS OF CRP

The acute phase response comprises the non-specific biochemical and physiological responses of endothermic animals to nearly every form of tissue damage, inflammation, neoplasia and infection.The synthesis of a number of protein is upregulated in hepatocytes under the influence of a cascade of cytokines, including, IL-6 ,IL-1 & TNF-α originating at the site of disease process.

CRP levels rapidly increase after inflammatory stimulus and depending upon the intensity of the stimulus, even a 100 fold increase in plasma levels may occur. CRP is not degraded to a significant extent in any process and its clearance is not influenced by any condition. Hence its concentration appears to be dependent on the rate of production and elimination. The $t^{1/2}$ is 19 hours, which is long and makes it's detection in blood after several hours of stimulus. Because of this nature of CRP, it is called as an “ideal marker of inflammation”.

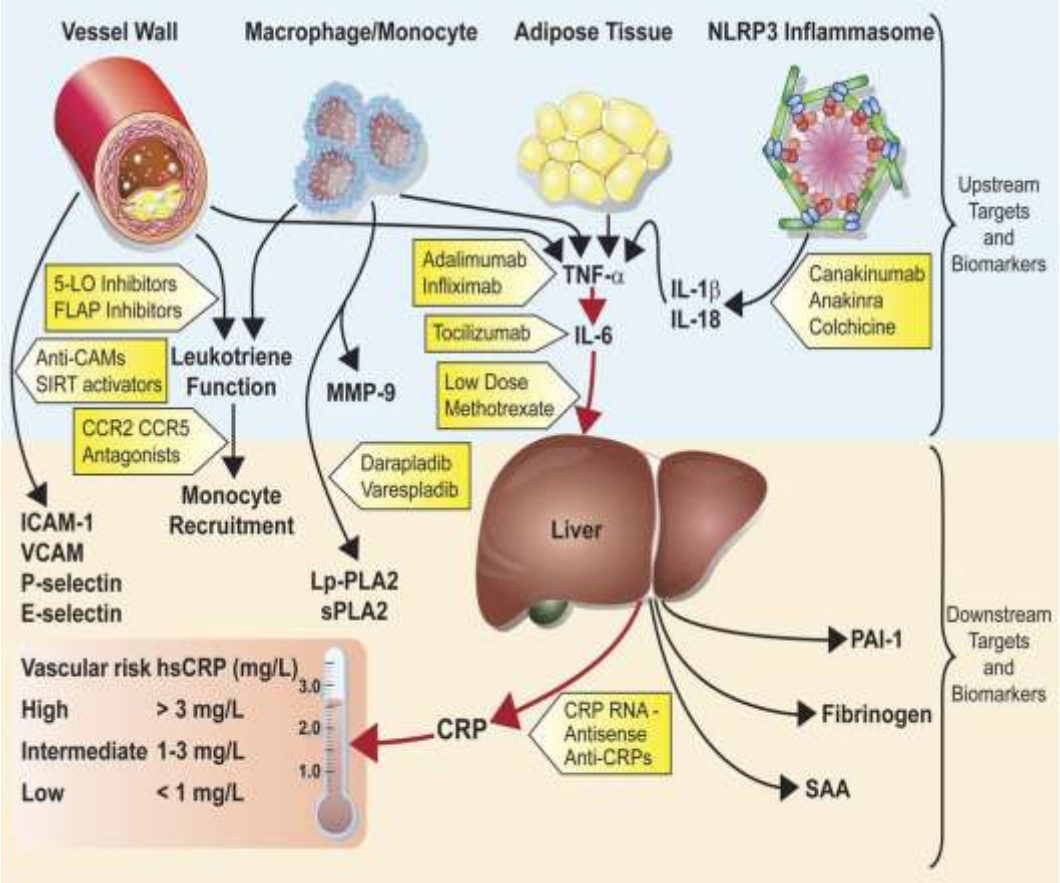
CRP VS OTHER ACUTE PHASE PROTEINS

Acute phase proteins includes, besides CRP, has other protein substances , such as albumin ,alpha 1 anti-trypsin , pro-calcitonin , ceruloplasmin , alpha 1 acid glycoprotein, fibrinogen, haptoglobin , alpha 2 haptoglobin, and Serum Amyloid A.

The disadvantage of the above mentioned proteins is that the difference in normal and pathological values are negligible. The values seen in those conditions are a few times than those found in healthy individuals.

Determination of SAA levels is difficult because of lack of methods to obtain routine measurements. CRP has an advantage that pathological values are easy to detect since the increase in concentration can be several hundred fold .

Liver generated CRP is stimulated by chemokines secreted by macrophages& monocytes. The rise in level of IL-6 concentration in serum is the earliest markers of inflammatory processes, detected within few hours after onset of infection. IL-6 concentration is usually detected 4 to 7 hours after the onset of infection, depending on the sensitivity of the method used to detect.



HIGH SENSITIVITY CRP (hs-CRP)

In 1990s, high sensitivity CRP assays started becoming available for measurement , allowing measurement of serum concentrations at the lower end . In the following years, hs-CRP levels were used , beneath the normal set value, indicating immediate-phase response, predicting the risk of diabetes mellitus, cerebrovascular disease, cognitive impairement and cardiovascular disease.

Normal reference range: 0.02 to 8.0 mg/L

	Unit	Normal	Moderate	High Risk
Hs-CRP	mg/dl	<1	1 - 3	>3
	mg/L	<10	10 - 30	>30

ROLE OF ACUTE PHASE REACTANTS IN ACUTE ISCHEMIC STROKE

Adipose tissue derived macrophages may be the primary source of many proinflammatory cytokines, like - CRP, IL -1 , 6 , 8 ; resistin , TNF – alpha. These are responsible for atheroma formation , which is the preliminary process in thrombus formation and which leads on to CVA/ACS.

Fibrinogen:

It's a soluble glycoprotein which constitutes 2-3% of plasma proteins, it consists of 4 polypeptide chains, it undergoes proteolytic cleavage to form thrombin, which is responsible for clot formation. Its used as marker in CVA to find out stroke severity and also in MI. It is a main component of plasma. It is involved in aggregation of platelets,

interactions between leucocytes and endothelial cells and primary hemostasis.

Normal level in plasma = 200-400mg/dl

Ferritin:

Ferritin is storage form of iron, it is stored in spleen, liver and bone marrow. It has a molecular weight of 4 lakhs, and can combine with 3000 atoms of iron. The maximum iron content of ferritin on weight basis is around 25%. There are studies about the role of serum iron in ischemic stroke. Studies revealing poor prognosis associated with high iron level.

Normal range: male – 12 to 300nanogram/ml,

Female- 12-150nanogram/ml

It has been well documented that increased serum ferritin level within 1 day of admission in hospital following stroke is associated with poor prognosis. Even high levels of serum ferritin in CSF are said to have grave prognosis in CVA patients.

CERULOPLASMIN:

It's a alpha 2 globulin synthesised in liver, contains 7 – 9 copper atoms per molecule. Responsible for iron incorporation into transferrin. Important anti-oxidant in plasma. It's an acute phase reactant, its

increased in all inflammatory conditions, collage vascular disease, and malignancies.

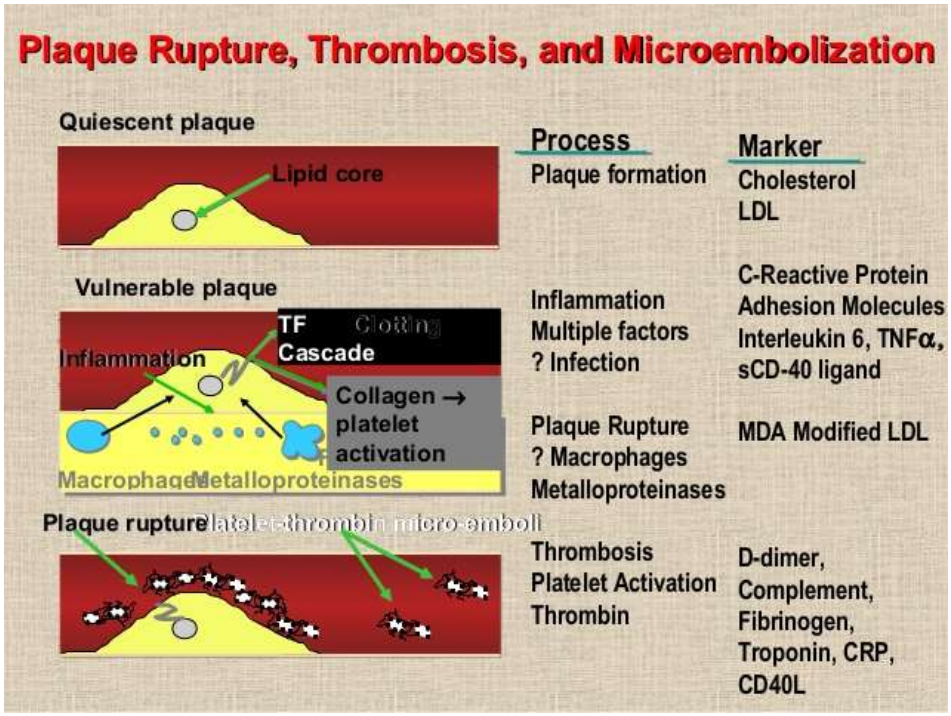
Normal Level in plasma – 25 to 50 mg/dl

CRP:

Increased level of hs-CRP is associated with adverse cerebrovascular and cardiovascular events. Increased CRP associated with high mortality following stoke and occurrence of first episode of stroke and carotid stenosis.

CRP AND ACS/CVA:

CRP has been used to understand the inflammatory components of atherosclerosis than other inflammatory mediators such as IL-6 & TNF –alpha. CRP has been researched over a decade in the role of atherosclerotic diseases. Its assessment can give an approach towards prognosis in ACS & CVA patients especially in first ever stroke.



FRAMINGHAM STUDY:

The study described the relationship between hs-CRP level and stroke incidents. It has been found out that among male patients who had high levels of hs CRP levels had 5 times higher incidence of CVA. Among female patients who had highest CRP levels during the time of study, had 14 times high risk of CVA , after following up for a period of 10 years. It has also been noted that those patients had 6 times more incidence of cardiaovascular and peripheral vascular events. Following the study , many studies were undertaken to prove this hypothesis.

RELATIONS OF hs-CRP TO VARIOUS VASCULAR EVENTS

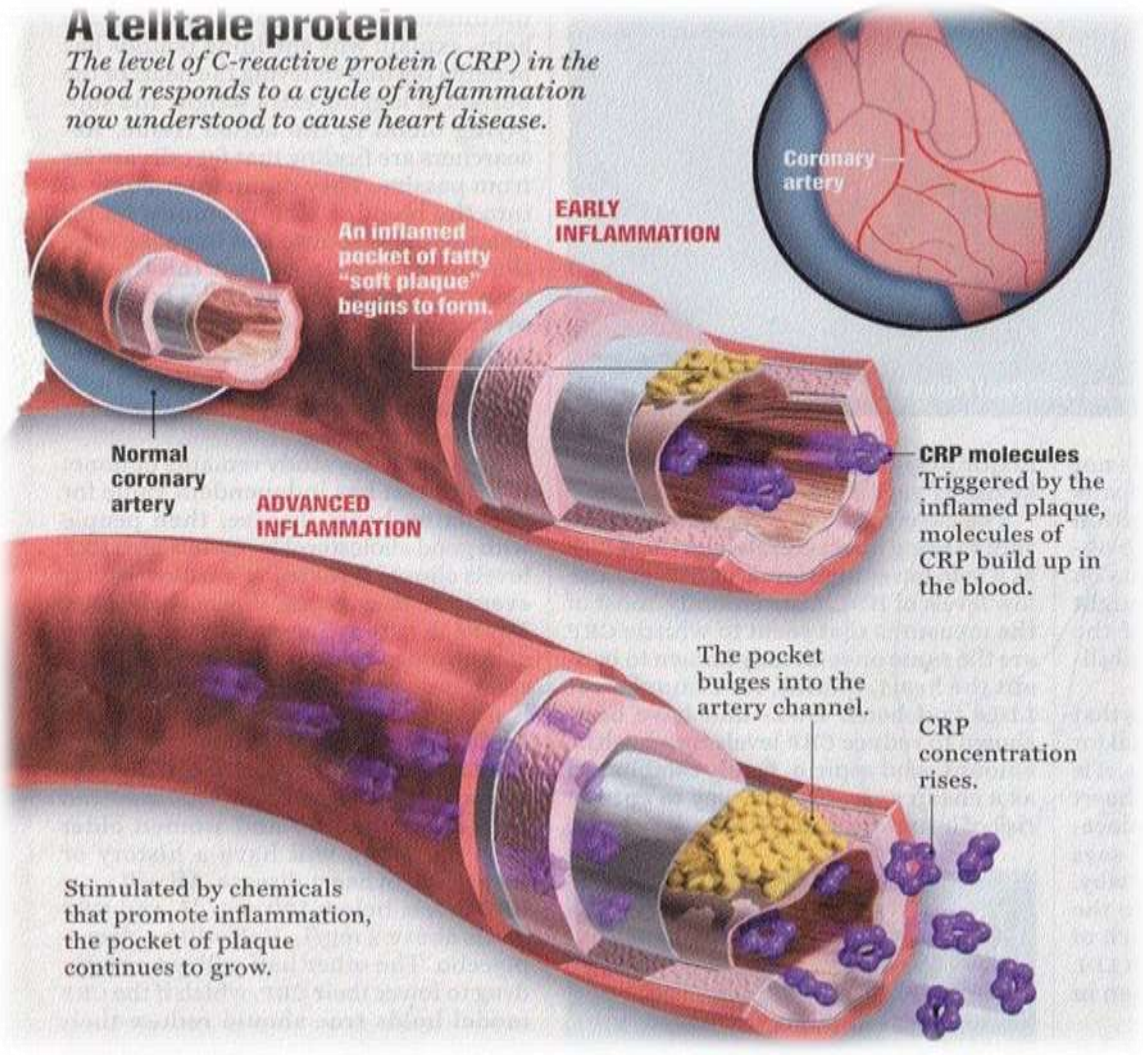
Baseline Level of C-Reactive Protein (mg/liter)				
Cardiovascular Disease During Follow-up	Geometric Mean	p	Median	p
None (N = 543)	1.10	--	1.13	--
Any Vascular Event (N = 246)	1.37	<0.001	1.40	<0.001
Myocardial Infarction (N = 246)	1.48	<0.001	1.51	<0.001
Any Stroke (N = 196)	1.30	0.03	1.36	0.03
Ischemic Stroke (N = 154)	1.36	0.01	1.38	0.02
Venous Thrombosis (N = 101)	1.24	0.22	1.26	0.34

There is rising evidence supporting that higher levels of hs-CRP is a predictor of cardiovascular disease and plays an vital role in the different stages of the development of atherosclerosis.

In normal subjects even a moderate increase of hs-CRP within the normal range (hs-CRP <5 mg/L) is considered to be predictive for a

variety of cardiovascular events, independent from other cardiovascular events

Many studies have shown significant relationship between high sensitive C-reactive protein with various cardiovascular risk factors like smoking,alcoholism,diabetes, hypertension,dyslipidemia and various other risk factors.



Correlations with other established risk factors including body mass index ,homocysteine, total cholesterol, triglycerides, age, systolic and diastolic blood pressure,number of cigarettes smoked per day,D-dimers, fibrinogen, and; CRP levels are related inversely with exercise frequency and high density lipoprotein (HDL) . CRP has emerged as a strong, independent risk factor.

A study was performed by So Yeon Ryu et al to evaluate the relation of hs-CRP with several cardiovascular risk factors such as white blood cell counts , smoking habit, blood pressure , blood glucose, serum lipids, body mass index,, routine exercise, alcohol drinking, age,in a cross-sectional survey. Plasma hs-CRP was measured by immunoturbidimetry in 202 subjects, aged over 50 years, who participated in health-check survey in a rural area of Jeollanamdo, Korea. Plasma hs-CRP level was 1.9 ± 3.0 mg/dL. He concluded that there were significant associations between hs-CRP levels and age, white blood cell counts, blood glucose, diastolic blood pressure, HDL-cholesterol, body mass index and smoking status. Though the correlation between plasma HDL-cholesterol and hs-CRP negatively significant, other blood lipid profile, such as total cholersetrol, LDL , TGL did not correlate sugnificantly.

With hs-CRP. Smoking is well supposed to give chemical and oxidative stress to cardiovascular system and cause inflammation. It has been reported that moderate alcohol consumption reduces circulating CRP. But in his study, the plasma hs-CRP level was not significantly affected by the alcohol drinking.

Increased levels of hs-CRP and intima-media thickness of the common carotid arteries are together shown to be associated with the occurrence of CVA. This was shown in a study conducted by Gulcin Benbir et al. He studied the relationship of increased hs-CRP levels with the extent of carotid atherosclerosis . He studied 104 patients aged between 30 to 92 yrs with acute ischemic stoke. The hs-CRP determination was performed 3 days after admission. The relationship between the hs-CRP level and the other risk factors were also evaluated in his study. All of the variables except HDL levels, failed to show a significant relationship with the hs-CRP levels. Only variable that showed a significant relation with the levels of the hs-CRP was HDL levels. It was shown that the major risk factors of the stroke were also associated with the higher levels of CRP and the treatment with antiplatelets and statins might have lowered the levels of CRP through their regulatory effects on the inflammation. High blood glucose, High

blood pressure, HDL cholesterol, as well as triglycerides were found to be strongly associated with CRP in a study by Blackburn R. *et al.*, (2001).

In a study by Choi *et al.*, 2004, there was no significant association between carotid atherosclerosis and hs-CRP in normotensive and hypertensive subjects.

Smokers had higher WBC, fibrinogen, and CRP levels in a study by Magyar *et al.* (2004). Several CHD risk factors appear to modulate the inflammatory response and affect hs-CRP concentration. Smokers have been shown to have increased concentration of several inflammatory markers, hs-CRP, including IL-6, and ICAM-1. Increased ICAM -1 and IL -6 a were shown to be associated with increased risk of future first coronary events in both men and women who smoke. Smoking cessation reduces these markers.

Diabetic patients are said to have increased hs-CRP levels, In this regard, links between hs-CRP and the insulin resistance syndrome have also been reported . In addition, experimental findings suggest that increased blood pressure accelerates endothelial expression of infammatory cytokines and other inflammatory mediators. These

observations suggest that perhaps better control of diabetes and hypertension may attenuate the contribution of the inflammatory response to overall cardiovascular risk. Taken together, the available evidence thus supports the hypothesis that hs-CRP concentrations correlate with endothelial dysfunction .

Also , another study by Liuzzo et al showed that in patients with severe unstable angina, hs-CRP concentrations >3 mg/L during hospi were associated with an increased incidence of recurrent angina, coronary revascularization, MI, and cardiovascular death.

In a similar study of unstable angina, Ferreiros et al concluded that the prognostic value of hs-CRP in predicting adverse outcome at 90 days.

A recent report by de Winter et al showed that hs-CRP concentrations >5 mg/L at admission in 150 patients with non-ST-elevation acute coronary syndromes were associated with an increased incidence of major cardiac events within 6 months .

Results from a population-based study in Russia The Arkhangelsk study conducted by M. Averina and his colleagues revealed U-shaped

association between hs-CRP and total alcohol intake. This U-shaped association became non-significant in both sexes after adjustment for age, BMI, smoking status, diabetes mellitus and cardiovascular medication.

Another study conducted by Chrysohoou et al in 2003, showed a U-shaped relation of several biochemical parameters related to atherosclerosis including hs-CRP and the amount of alcoholic beverages consumed.

A study by Rasouli Mehdi et al in 2006 , showed that elevated hs-CRP was assosciated with male sex, diabetes, hypertension and high levels of serum glucose.

Another study by Minna Soinio et al concluded that diabetic patients have higher levels of hs-CRP than people without diabetes and that elevated hs-CRP levels are an independent risk factor for death from CHD in people with diabetes

MATERIALS

AND

METHODS

MATERIALS AND METHODS

Setting:

Medical ward , Govt. Kilpauk Medical College, Chennai.

Study design:

Prospective hospital based study.

Period of study:

Jan 2015 to June 2015

Inclusion criteria:

1. All patients who presented within 48 hours of onset of stroke and who gave informed consent to participate in the study were included.

Exclusion criteria:

1. Subarachnoid haemorrhage, subdural haemorrhage and intracerebral haemorrhage were excluded with the aid of CT scan.
2. Patients above 70 years of age were excluded.
3. Patients with evidence of active infection and neoplastic conditions at the time of study were excluded.

4. Patients with rheumatic heart disease and collagen vascular disease were excluded.
5. Patients who were actively smoking at the time of study were excluded.
6. Patients with previous history of transient ischemic attack or reversible ischemic neurological deficit were excluded.

Study method:

A total of 50 patients who presented with acute ischemic stroke were enrolled into the study. That the stroke was an ischemic one was confirmed by CT scan. As soon as the patients were admitted within 48 hours of onset of stroke, serum samples were taken for hs-CRP estimation. Serum hs-CRP levels were also estimated in fifty normal patients (without any evidence of acute infection, neoplasm, rheumatic heart disease, collagen vascular disease, hypertension, DM, IHD) and was found to be within normal limits.

Standard guidelines for the treatment of acute ischemic stroke were followed. None of the patients received any thrombolytic treatment. They were treated only with antiedema measures and antiplatelets such as aspirin alone and with good nursing care and physiotherapy.

The patients were reviewed after 4 weeks after onset of stroke and were stratified using the Glasgow Outcome Scale (GOS). The serum hs-CRP level was correlated with the functional recovery of patients after 4 weeks using the GOS. Patients with score of 4 and 5 were included in the good outcome and patients with score of 1, 2, 3 were included in the poor outcome cateogory.

Definitions followed in the Study:

1. **Stroke**

Stroke (as defined by WHO) was defined as rapidly developing clinical signs of focal or global (for patients in coma) neurological deficit lasting more than 48 hours or leading to death with no apparent cause other than vascular origin.

2. hs-CRP:

Cut off value for hs-CRP for assessing the prognosis of stroke in this study was taken as ≥ 10.1 mg/L and the serum hs-CRP level was correlated with the functional recovery of patients after 4 weeks using the GOS. This was based on a study by Muir KW et al who found that hs-CRP levels above 10.1mg/L when measured within 72 hours of stroke predicted mortality over 4 years[102].

3. GOS:

The GOS was utilized to assess the functional outcome and residual neurological deficit. The GOS has frequently been used in trials involving stroke and brain injuries. It is a well validated scale with good interobserver agreement.

GLASGOW OUTCOME SCALE (GOS):

1 - indicates death

2 - a vegetative state (the patient is unable to interact with the environment)

3 - severe disability (the patient is unable to live independently but can follow commands)

4 - moderate disability (the patient is capable of living independently but unable to return to work or school)

5 - mild or no disability (the patient is able to to return to work or school)

Favourable outcome was defined as a score of 4 or 5 and unfavourable outcome as a score of 1, 2 , or 3.

4. Hypertension:

Hypertension in this study was taken as BP ≥ 140/90 mmHg as per JNC VIII

MEASUREMENT OF hs-CRP

The Quantia CRP-US (from Tulip Diagnostics Pvt. Ltd) was used for the measurement of hs-CRP. Quantia CRP is a turbidimetric immunoassay for ultrasensitive determination of CRP in human serum and is based on the principle of agglutination reaction . The test specimen is mixed with quantia CRP US latex reagent and activation buffer and allowed to react. Presence of CRP in the test specimen results in the formation of an insoluble complex producing a turbidity, which is measured at wavelength between 505-578 nm. The increase in turbidity corresponds to the concentration of CRP in the test specimen.

Test procedure:

400 microlitre of quantia CRP US activation buffer (R1) was pipetted out and added to 100 microlitre of Quantia CRP US latex reagent (R2) in the measuring cuvette. It was mixed well and incubated for 5 minutes. 5 microlitre of test specimen was added and mixed gently. Absorbance (A1) was read exactly at 10 seconds and absorbance (A2)

was read again at the end of exactly 4 minutes. ΔA (A2-A1) for test specimen was calculated.

ΔA gives the CRP concentration ('C') of the test specimen.

The CRP concentration C was multiplied with the dilution factor (F) of the test specimen for obtaining the concentration of CRP in the test specimen.

Concentration of CRP in the test specimen in mg/dl=C x F,

(where F is the dilution factor of the test specimen)

The quantia CRP US reagent has been designed to measure CRP concentrations in the range of 0.015-1.0 mg/dl and is linear within the measuring range.

RESULTS AND ANALYSIS

STATISTICAL ANALYSIS:

The collected data was analysed with SPSS 16.0 version.To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups (Male & Female) Unpaired sample t-test was used. To find the significance in categorical data Chi-Square test was used. In both the above statistical tools the probability value .05 is considered as significant level.

P - Value	Highly Significant at P ≤ .01

P - Value	Significant at P ≤ .05

P -Value	No Significant at P ≥ .05

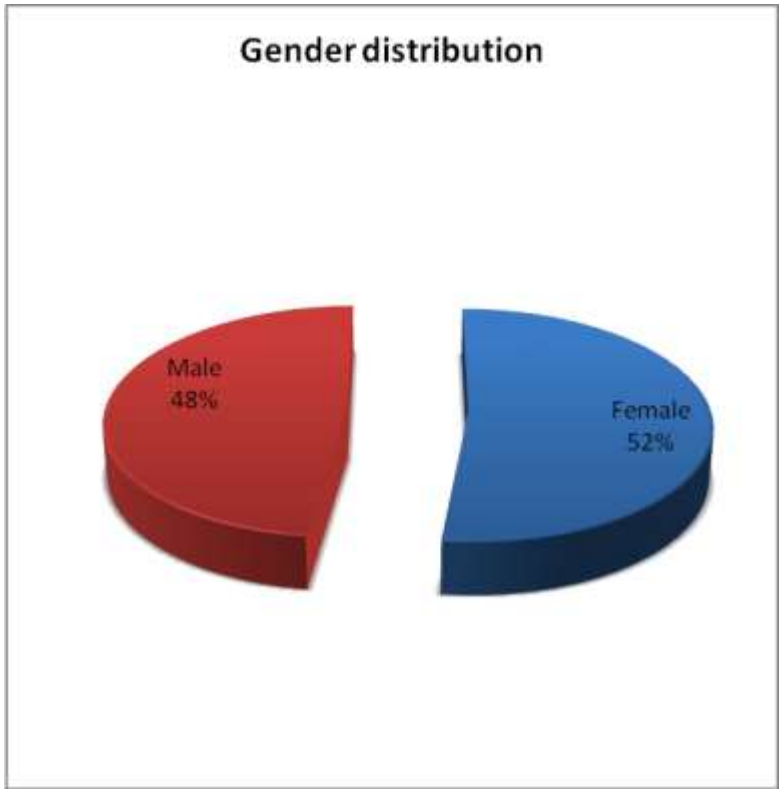
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	26	52.0	52.0	52.0
	Male	24	48.0	48.0	100.0
	Total	50	100.0	100.0	

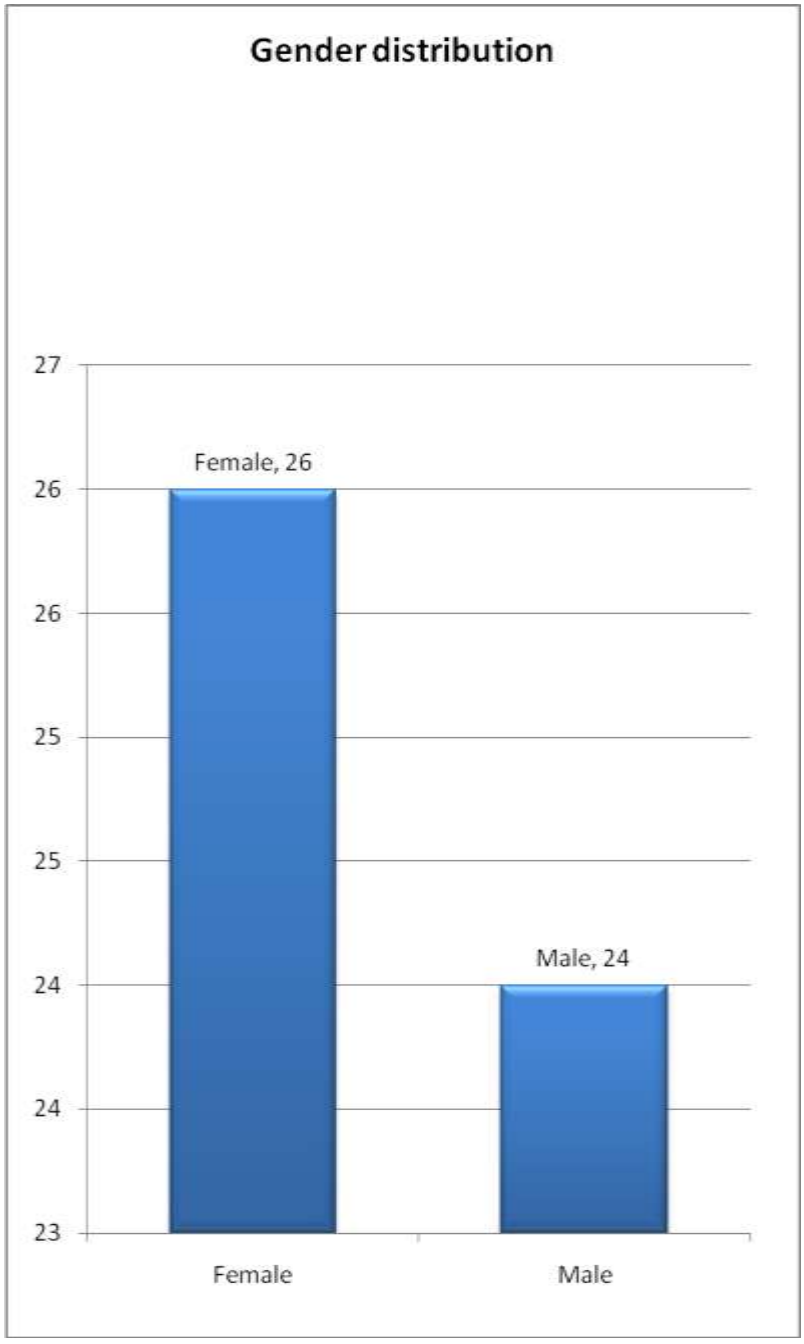
Descriptive studies

	No	Maximum	Minimum	Mean	Std.deviation
Age valid N(listwise	50 50	45	70	59.90	7.360

	No	Maximum	Minimum	Mean	Std.deviation
Age valid N(listwise	26 26	47	70	60.65	6.852

	No	Maximum	Minimum	Mean	Std.deviation
Age valid N(list wise)	24 24	45	70	59.08	7.940


Gender distribution
Male
48%
Female
52%


Gender distribution
27
26
26
25
25
24
24
23
Female, 26
Male, 24
Female
Male

SEX * SSCORE

			SSCORE		
			Favourable	Unfavourable	Total
SEX	F	Count	12	14	26
		% within SSCORE	66.7%	43.8%	52.0%
	M	Count	6	18	24
		% within SSCORE	33.3%	56.3%	48.0%
Total		Count	18	32	50
		% within SSCORE	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.424[a]	1	.119		
Continuity Correction[b]	1.593	1	.207		
Likelihood Ratio	2.460	1	.117		
Fisher's Exact Test				.149	.103
N of Valid Cases	50				

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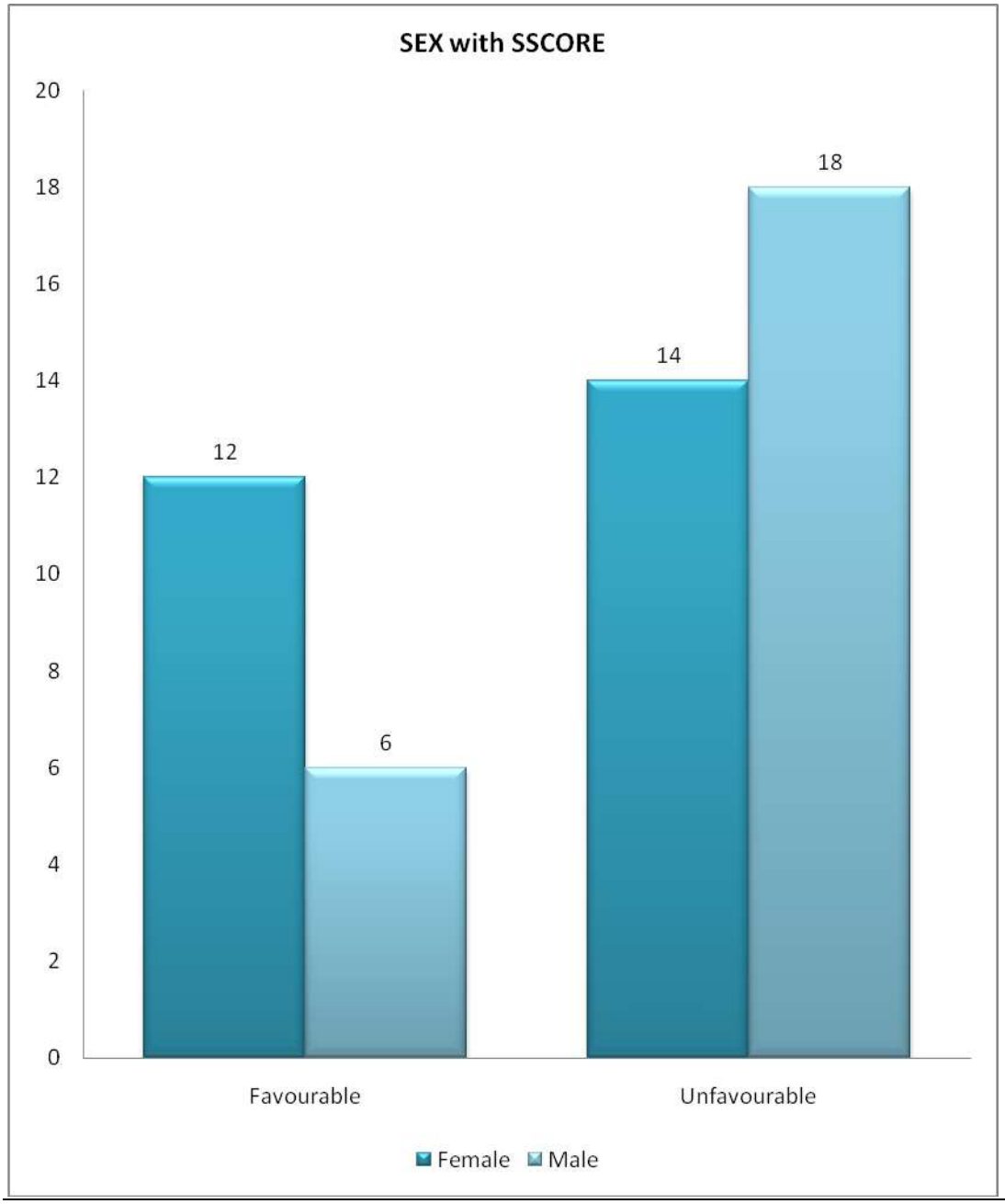
	Favourable	Unfavourable
Female	12	14
Male	6	18



SEX * Hs-CRP LEVEL range

Crosstab

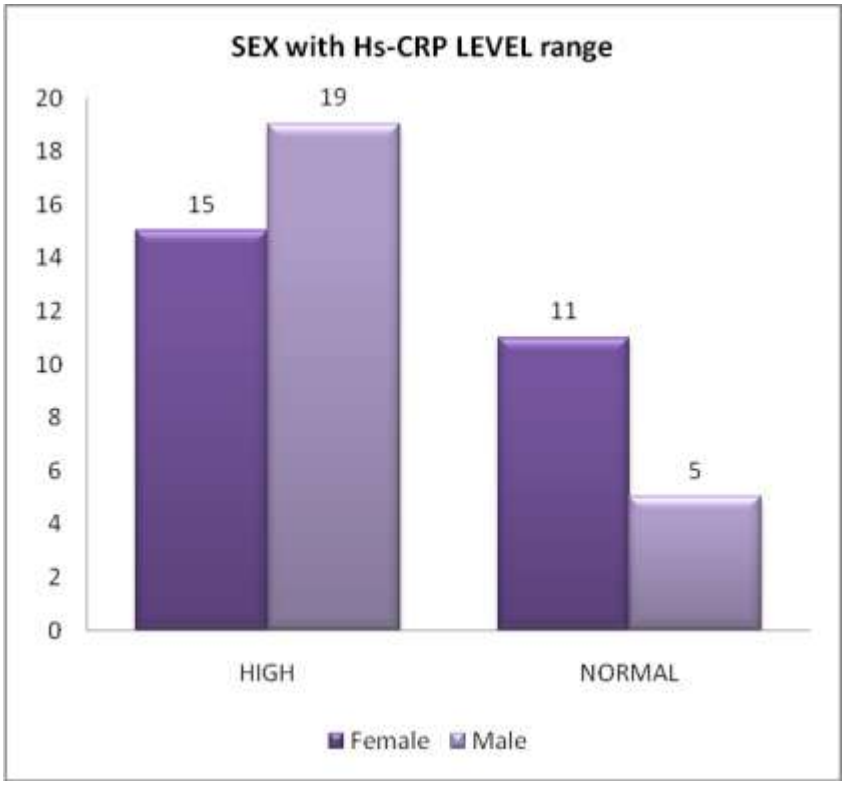
			Hs-CRP LEVEL range		
			HIGH	NORMAL	Total
SEX	F	Count	15	11	26
		% within Hs-CRP LEVEL range	44.1%	68.8%	52.0%
	M	Count	19	5	24
		% within Hs-CRP LEVEL range	55.9%	31.3%	48.0%
Total		Count	34	16	50
		% within Hs-CRP LEVEL range	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.645a	1	.104		

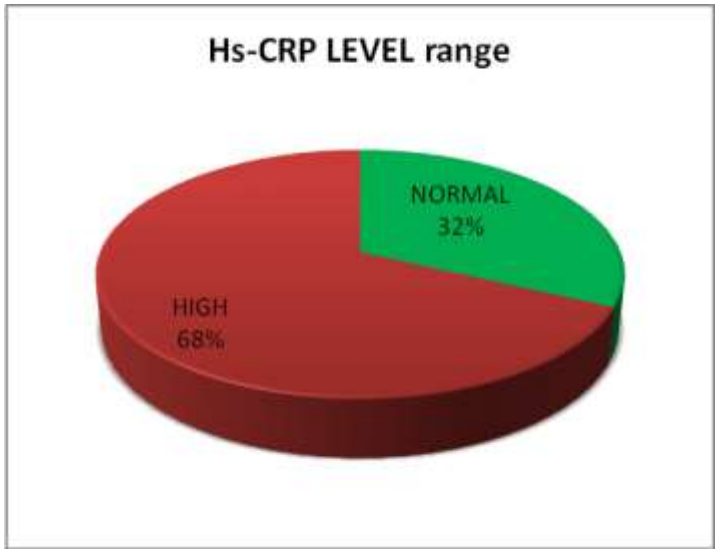
Continuity Correctionb	1.750	1	.186		
Likelihood Ratio	2.698	1	.100		
Fisher's Exact Test				.135	.092
N of Valid Cases	50				

	HIGH	NORMAL
Female	15	11
Male	19	5



Hs-CRP LEVEL range

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NORMAL	16	32.0	32.0	32.0
	HIGH	34	68.0	68.0	100.0
	Total	50	100.0	100.0	



Time of sample collection

	No	Mean in hrs	SD	Std.error of mean
Time of sample collection	50	13.96	9.95	1.048

Hs-CRP LEVEL range * SSCORE

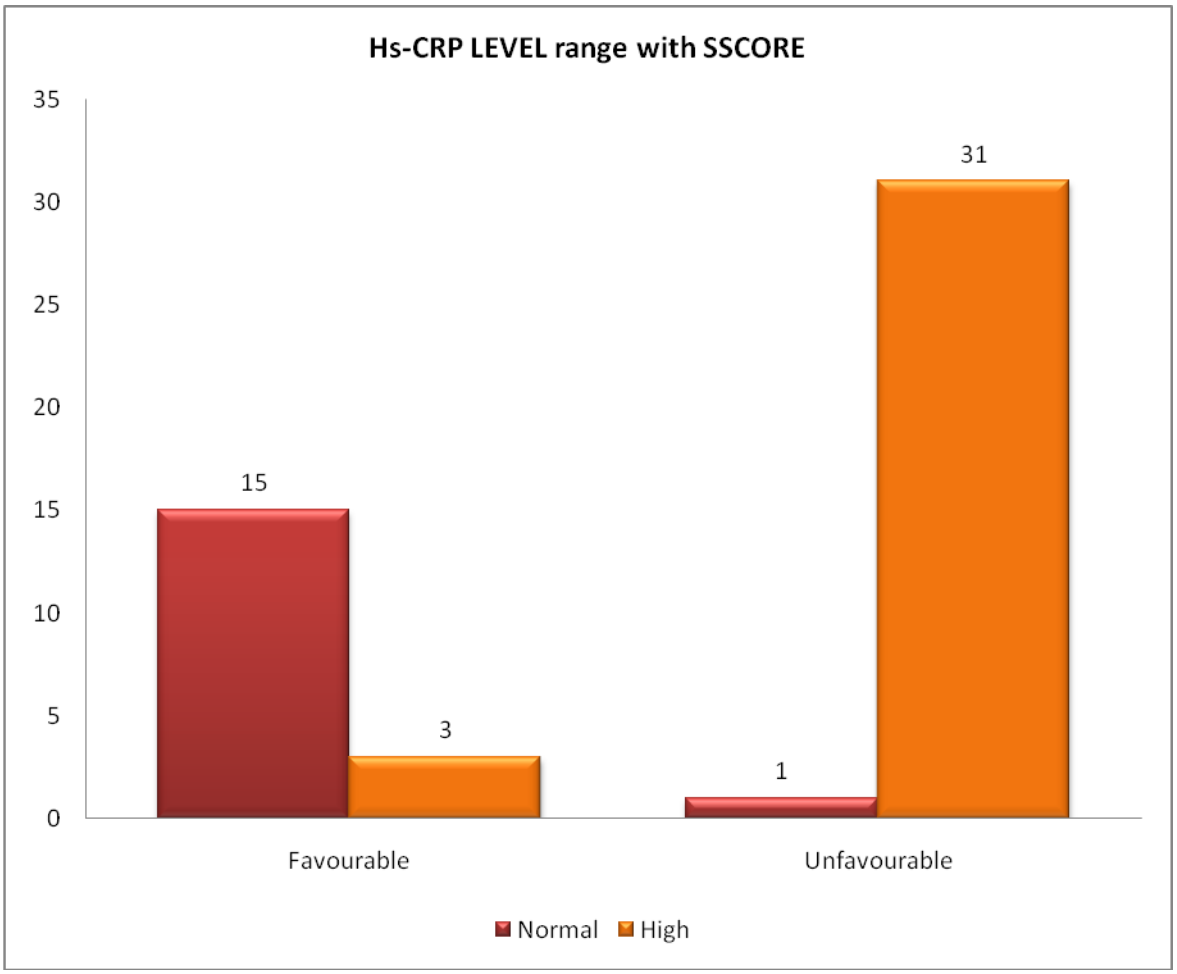
Crosstab

			SSCORE			
			Favourable	Unfavourable	Total	
Hs-CRP LEVEL range	NORMAL	Count	15	1	16	
		% within SSCORE	83.3%	3.1%	32.0%	
	HIGH	Count	3	31	34	
		% within SSCORE	16.7%	96.9%	68.0%	
Total		Count	18	32	50	
		% within SSCORE	100.0%	100.0%	100.0%	

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	34.059[a]	1	.000		
Continuity Correction[b]	30.473	1	.000		
Likelihood Ratio	37.567	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	33.378	1	.000		
N of Valid Cases	50				

	Favourable	Unfavourable
Normal	15	1
High	3	31



Group Statistics

Hs-CRP LEVEL range		N	Mean	Std. Deviation	Std. Error Mean
AGE	NORMAL	16	57.9	6.971	1.743
	HIGH	34	60.8	7.457	1.279

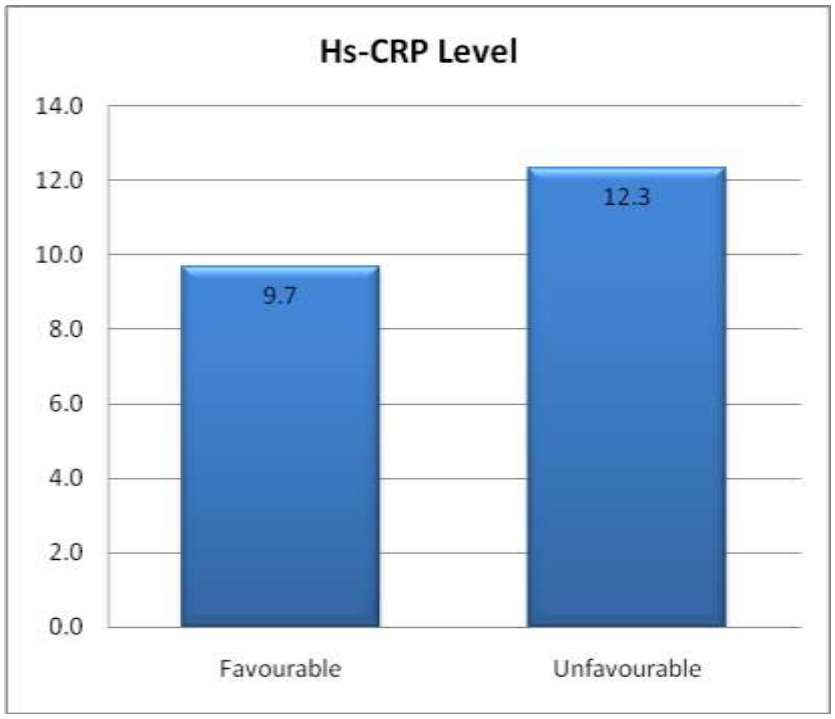
		Levene's Test for Equality of Variances		t-test for Equality of Means							
									95% Confidence Interval of the Difference		
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper	
AGE	Equal variances assumed	.172	.680	-1.303	48	.199	-2.886	2.216	-7.341	1.569	
	Equal variances not assumed			-1.335	31.369	.191	-2.886	2.162	-7.293	1.521	

Group Statistics

SSCORE		N	Mean	Std. Deviation	Std. Error Mean
Hs-CRP LEVEL	Favourable	18	9.7	1.5761	.3715
	Unfavourable	32	12.3	1.8531	.3276

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Hs-CRP LEVEL	Equal variances assumed	.643	.427	-5.123	48	.000	-2.6566	.5185	-3.6992	-1.6140
	Equal variances not assumed			-5.364	40.340	.000	-2.6566	.4953	-3.6574	-1.6558



SMOKER

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	29	58.0	58.0	58.0
	YES	21	42.0	42.0	100.0
	Total	50	100.0	100.0	

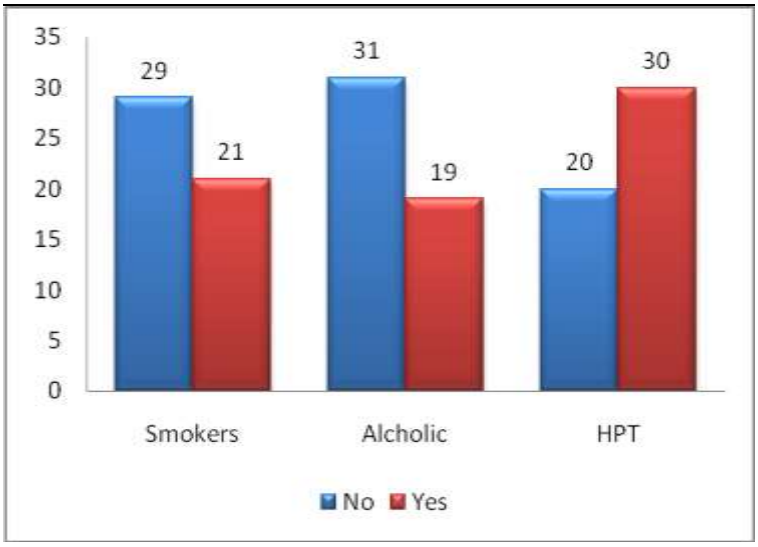
ALCOHOLIC

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	31	62.0	62.0	62.0
	YES	19	38.0	38.0	100.0
	Total	50	100.0	100.0	

HYPERTENSION

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	20	40.0	40.0	40.0
	YES	30	60.0	60.0	100.0
	Total	50	100.0	100.0	

	Smokers	Alcholic	HPT
No	29	31	20
Yes	21	19	30



SMOKER * Hs-CRP LEVEL range

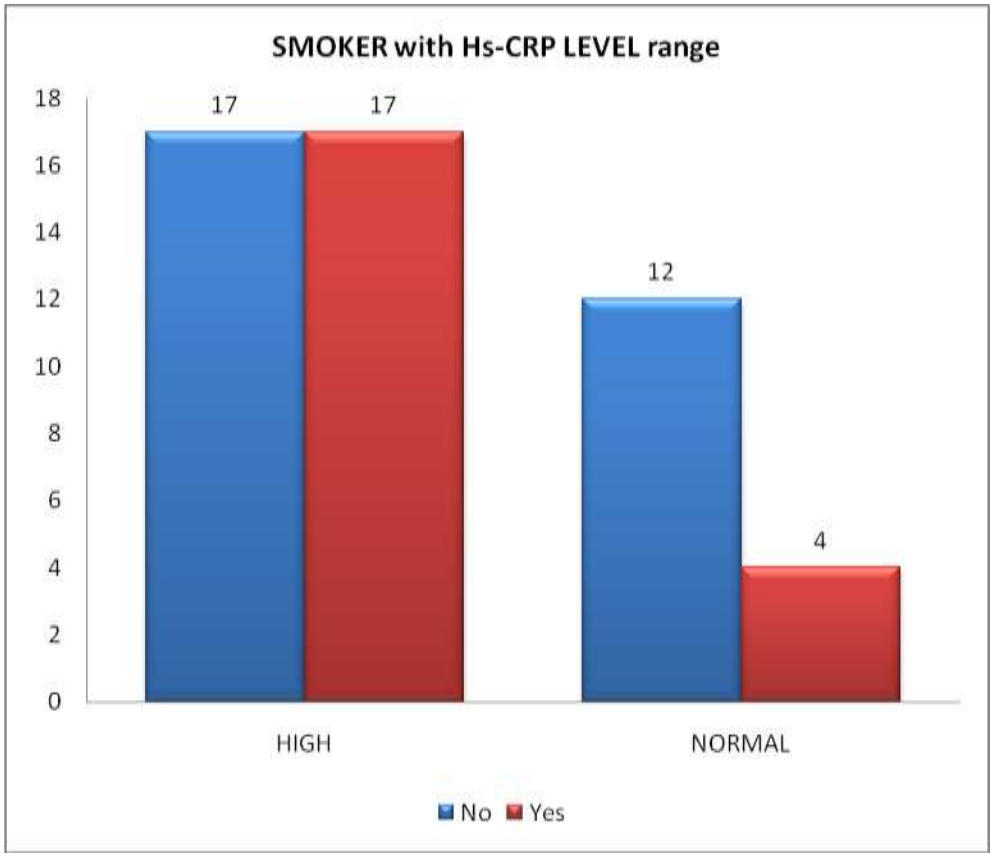
Crosstab

			Hs-CRP LEVEL range		
			HIGH	NORMAL	Total
SMOKER	NO	Count	17	12	29
		% within Hs-CRP LEVEL range	50.0%	75.0%	58.0%
	YES	Count	17	4	21
		% within Hs-CRP LEVEL range	50.0%	25.0%	42.0%
Total		Count	34	16	50
		% within Hs-CRP LEVEL range	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.791[a]	1	.095		
Continuity Correction[b]	1.860	1	.173		
Likelihood Ratio	2.900	1	.089		
Fisher's Exact Test				.129	.085
N of Valid Cases	50				

	HIGH	NORMAL
No	17	12
Yes	17	4



SMOKER * SSCORE

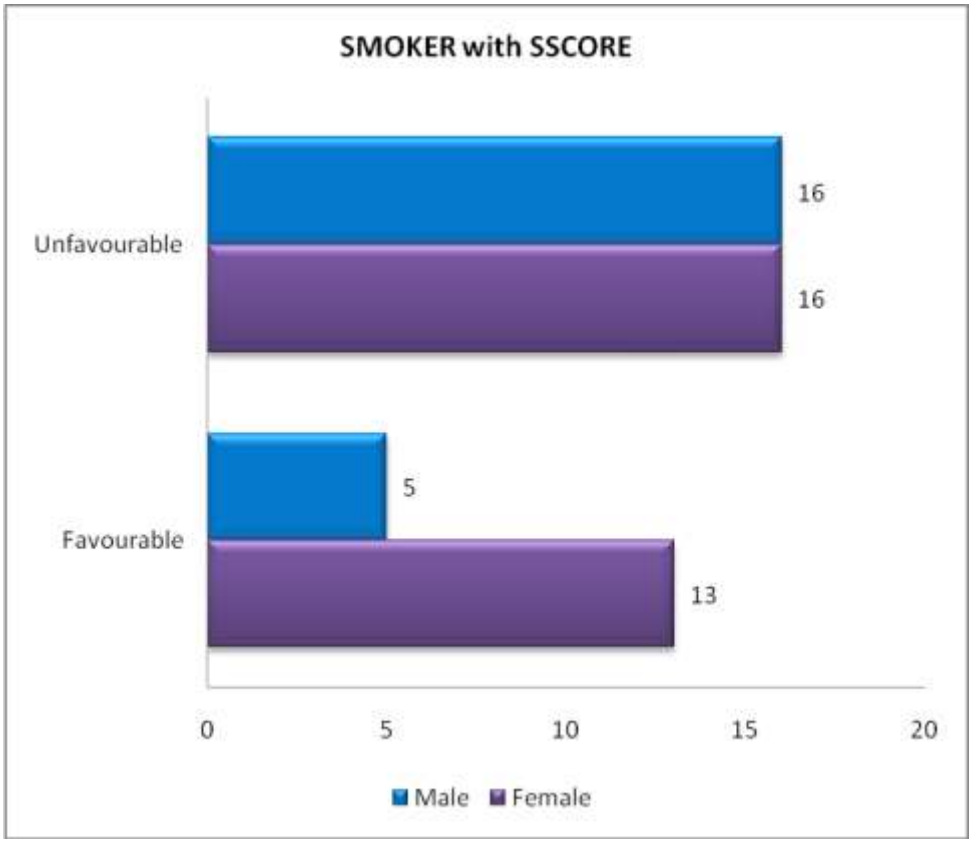
Crosstab

			SSCORE		
			Favourable	Unfavourable	Total
SMOKER	NO	Count	13	16	29
		% within SSCORE	72.2%	50.0%	58.0%
	YES	Count	5	16	21
		% within SSCORE	27.8%	50.0%	42.0%
Total		Count	18	32	50
		% within SSCORE	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.335[a]	1	.126		
Continuity Correction[b]	1.512	1	.219		
Likelihood Ratio	2.397	1	.122		
Fisher's Exact Test				.149	.109
N of Valid Cases	50				

	Favourable	Unfavourable
Female	13	16
Male	5	16



ALCOHOLIC * Hs-CRP LEVEL range

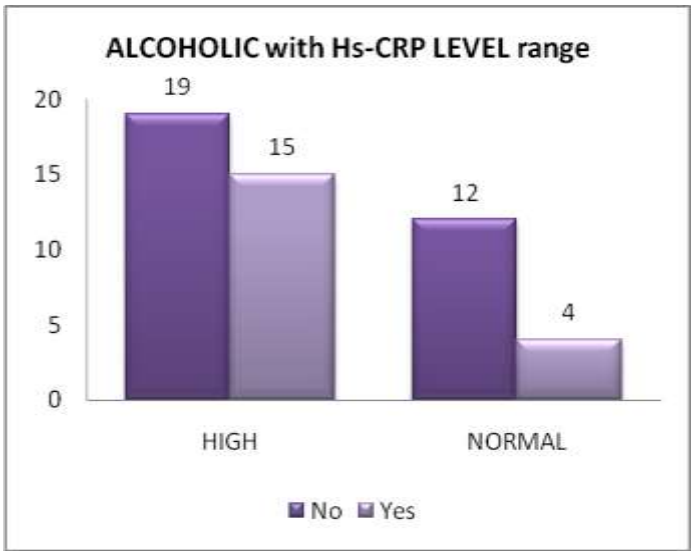
Crosstab

			Hs-CRP LEVEL range		
			HIGH	NORMAL	Total
ALCOHOLIC	NO	Count	19	12	31
		% within Hs-CRP LEVEL range	55.9%	75.0%	62.0%
	YES	Count	15	4	19
		% within Hs-CRP LEVEL range	44.1%	25.0%	38.0%
Total		Count	34	16	50
		% within Hs-CRP LEVEL range	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.688[a]	1	.194		
Continuity Correction[b]	.974	1	.324		
Likelihood Ratio	1.749	1	.186		
Fisher's Exact Test				.228	.162
N of Valid Cases	50				

	HIGH	NORMAL
No	19	12
Yes	15	4



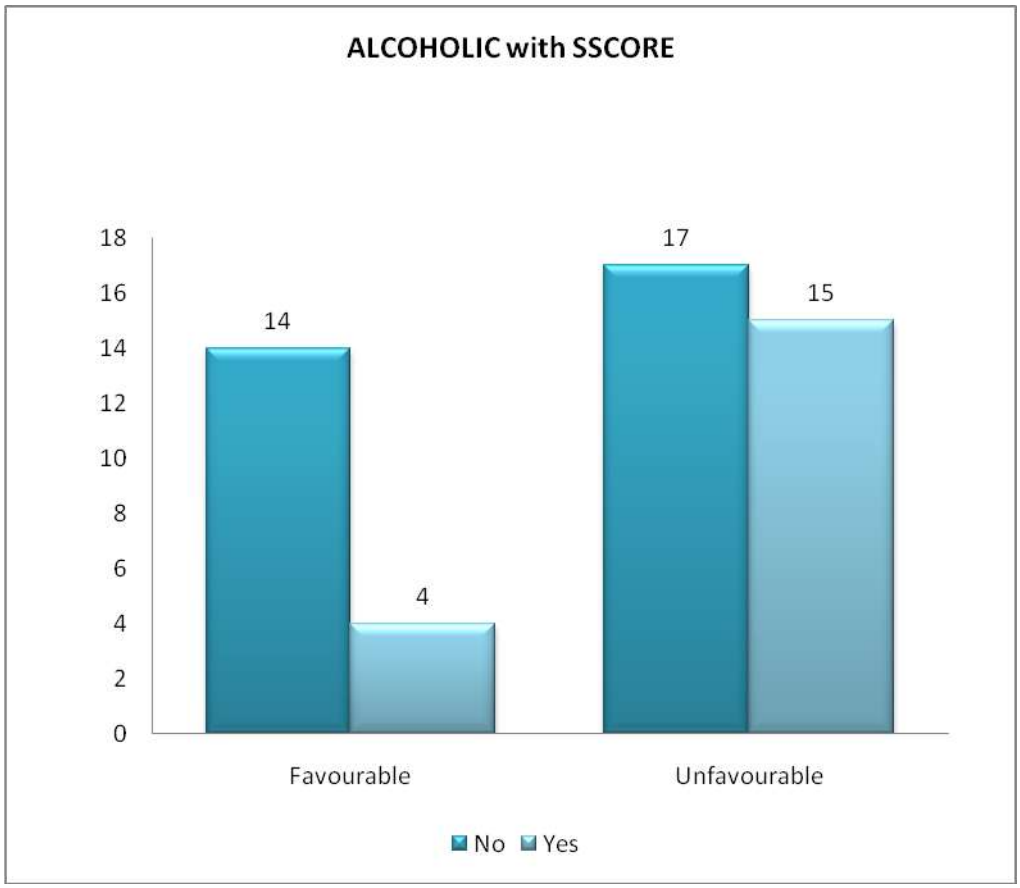
Crosstab

			SSCORE		Total
Favourable	Unfavourable				
ALCOHOLIC	NO	Count	14	17	31
		% within SSCORE	77.8%	53.1%	62.0%
	YES	Count	4	15	19
		% within SSCORE	22.2%	46.9%	38.0%
Total		Count	18	32	50
		% within SSCORE	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.972[a]	1	.085		
Continuity Correction[b]	2.017	1	.155		
Likelihood Ratio	3.101	1	.078		
Fisher's Exact Test				.130	.076
N of Valid Cases	50				

	Favourable	unfavaurable
Yes	4	15
no	14	17



HYPERTENSION * Hs-CRP LEVEL range

Crosstab

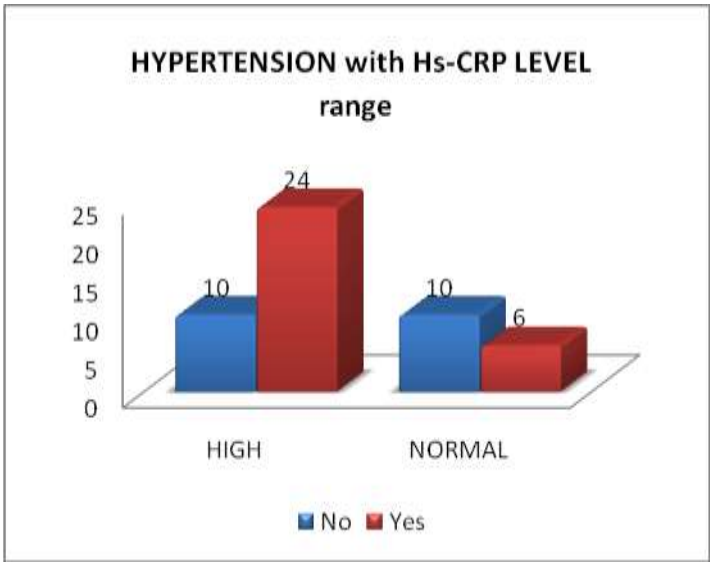
			Hs-CRP LEVEL range		
			HIGH	NORMAL	Total
HYPERTENSION	NO	Count	10	10	20
		% within Hs-CRP LEVEL range	29.4%	62.5%	40.0%
	YES	Count	24	6	30
		% within Hs-CRP LEVEL range	70.6%	37.5%	60.0%
Total		Count	34	16	50
		% within Hs-CRP LEVEL range	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.963[a]	1	.026		

Continuity Correction[b]	3.680	1	.055		
Likelihood Ratio	4.937	1	.026		
Fisher's Exact Test				.034	.028
N of Valid Cases	50				

	HIGH	NORMAL
No	10	10
Yes	24	6



HYPERTENSION * SSCORE

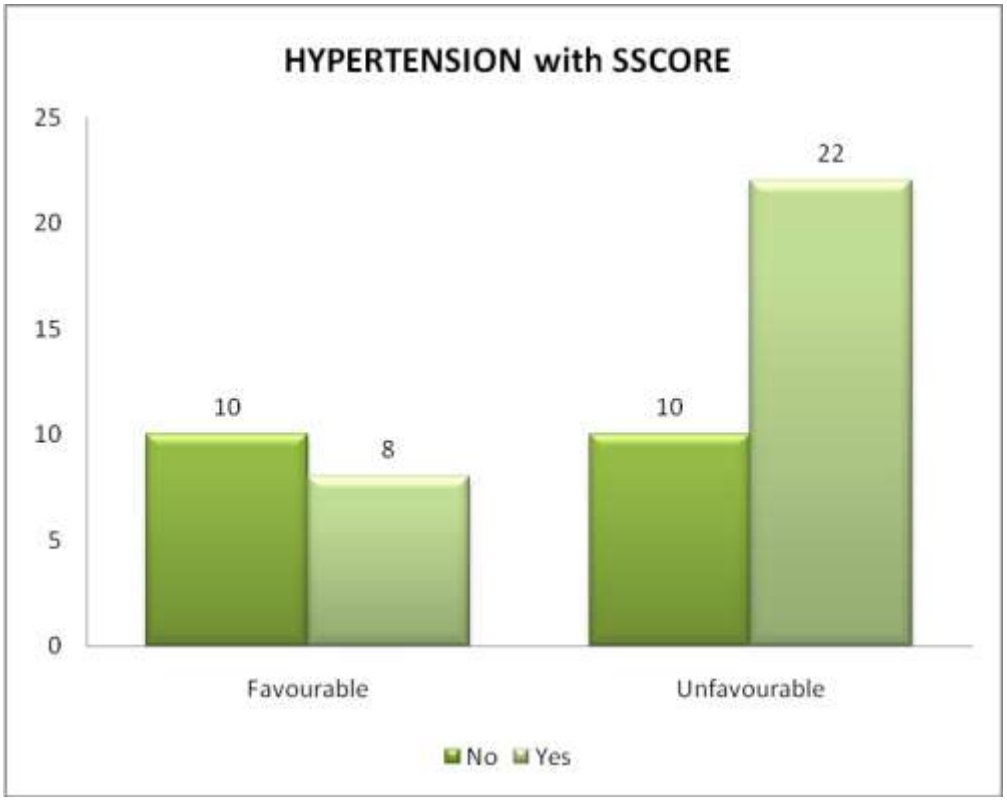
Crosstab

			SSCORE		
			Favourable	Unfavourable	Total
HYPERTENSION	NO	Count	10	10	20
		% within SSCORE	55.6%	31.3%	40.0%
	YES	Count	8	22	30
		% within SSCORE	44.4%	68.8%	60.0%
Total		Count	18	32	50
		% within SSCORE	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.836[a]	1	.092		
Continuity Correction[b]	1.913	1	.167		
Likelihood Ratio	2.821	1	.093		
Fisher's Exact Test				.134	.084
N of Valid Cases	50				

	Favourable	Unfavourable
No	10	10
Yes	8	22



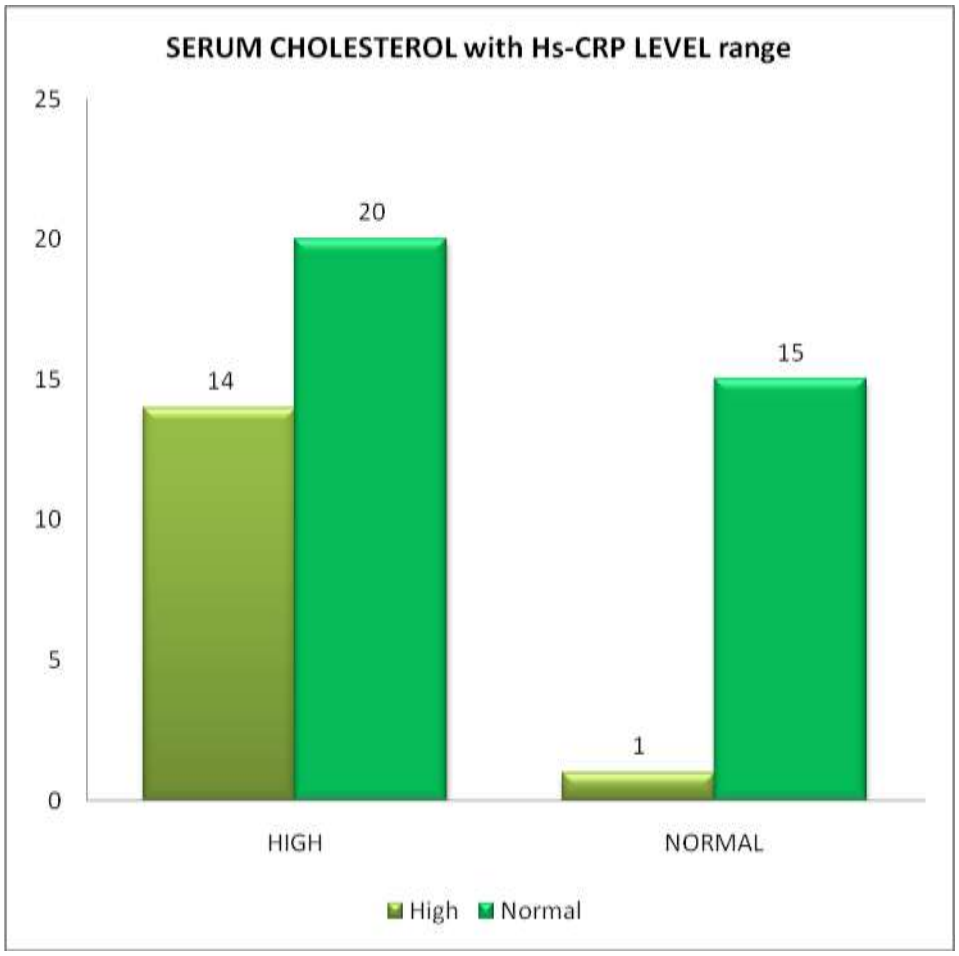
SERUM CHOLESTEROL * Hs-CRP LEVEL range

Crosstab

			Hs-CRP LEVEL range		
			HIGH	NORMAL	Total
SERUM CHOLESTEROL	HIGH	Count	14	1	15
		% within Hs-CRP LEVEL range	41.2%	6.3%	30.0%
	NORMAL	Count	20	15	35
		% within Hs-CRP LEVEL range	58.8%	93.8%	70.0%
Total		Count	34	16	50
		% within Hs-CRP LEVEL range	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.320[a]	1	.012		
Continuity Correction[b]	4.766	1	.029		
Likelihood Ratio	7.535	1	.006		
Fisher's Exact Test				.019	.011
N of Valid Cases	50				

	HIGH	NORMAL
High	14	1
Normal	20	15



SERUM CHOLESTEROL * SSCORE

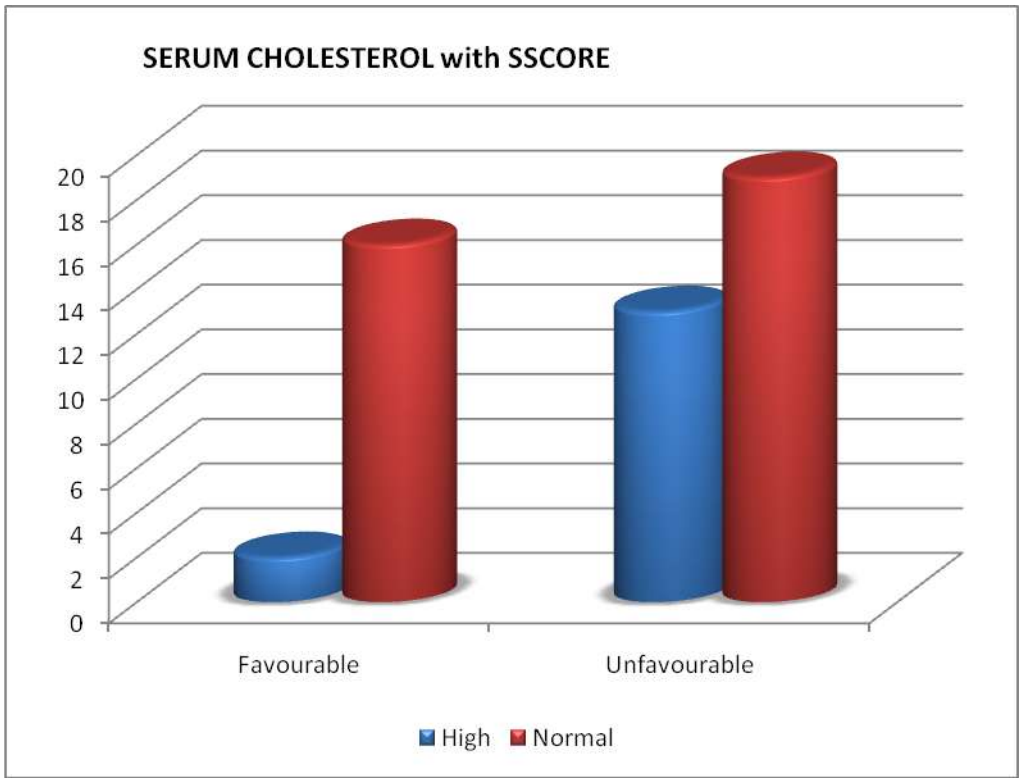
Crosstab

			SSCORE		
			Favourable	Unfavourable	Total
SERUM CHOLESTEROL	HIGH	Count	2	13	15
		% within SSCORE	11.1%	40.6%	30.0%
	NORMAL	Count	16	19	35
		% within SSCORE	88.9%	59.4%	70.0%
Total		Count	18	32	50
		% within SSCORE	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.778[a]	1	.029		
Continuity Correction[b]	3.476	1	.062		
Likelihood Ratio	5.299	1	.021		
Fisher's Exact Test				.052	.028
N of Valid Cases	50				

	Favourable	Unfavourable
High	2	13
Normal	16	19



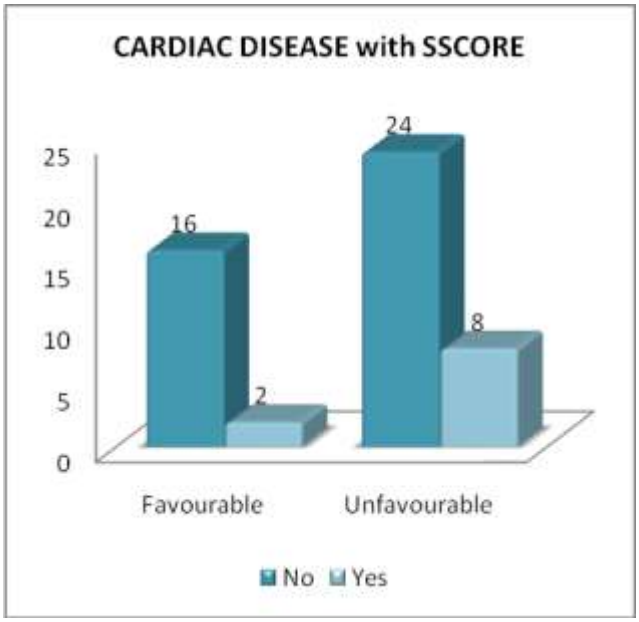
CARDIAC DISEASE * SSCORE

Crosstab

			SSCORE		
			Favourable	Unfavourable	Total
CARDIAC DISEASE	NO	Count	16	24	40
		% within SSCORE	88.9%	75.0%	80.0%
	YES	Count	2	8	10
		% within SSCORE	11.1%	25.0%	20.0%
Total		Count	18	32	50
		% within SSCORE	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.389[a]	1	.239		
Continuity Correction[b]	.656	1	.418		
Likelihood Ratio	1.493	1	.222		
Fisher's Exact Test				.295	.212
N of Valid	50				



	favourable	unfavourable
no	16	24
yes	2	8

Cardiac disease

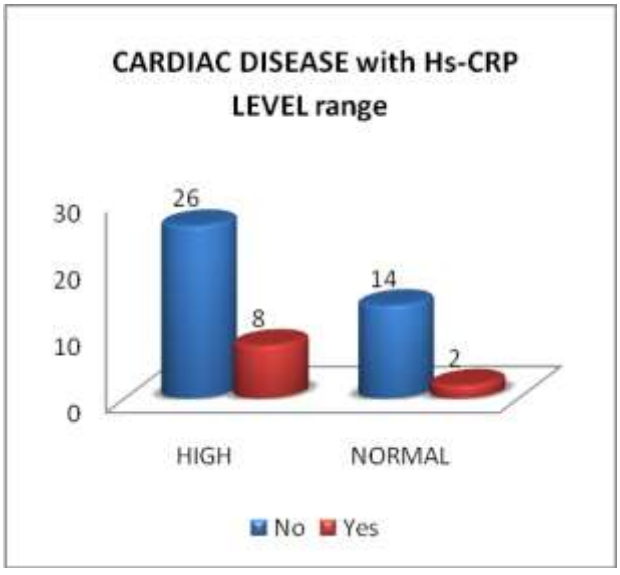
Crosstab

		Hs-CRP LEVEL range		
		HIGH	NORMAL	Total
CARDIAC DISEASE NO	Count	26	14	40
	% within Hs-CRP LEVEL range	76.5%	87.5%	80.0%
YES	Count	8	2	10
	% within Hs-CRP LEVEL range	23.5%	12.5%	20.0%
Total	Count	34	16	50
	% within Hs-CRP LEVEL range	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.827[a]	1	.363		
Continuity Correction[b]	.281	1	.596		
Likelihood Ratio	.883	1	.347		
Fisher's Exact Test				.468	.307
N of Valid Cases	50				

	HIGH	NORMAL
No	26	14
Yes	8	2



SSCORE

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Favourable	18	36.0	36.0	36.0
	Unfavourable	32	64.0	64.0	100.0
	Total	50	100.0	100.0	

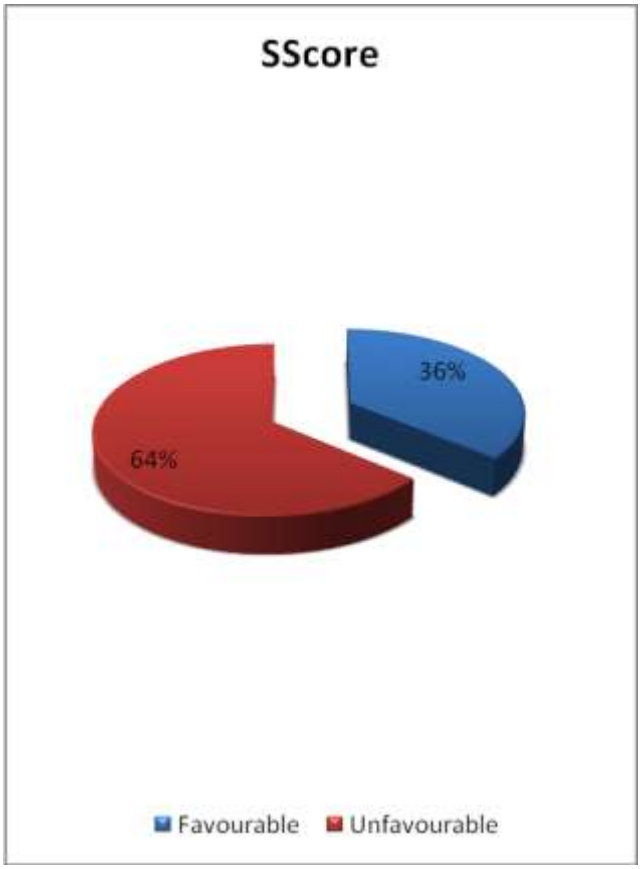


Table 12: hs-CRP Vs GOS Score

GOS	hs-CRP (mg/L)		Total
	< 10.1	**≥10.1**	
1	0(0%)	2(4%)	2(4%)
2	0(0%)	13(26%)	13(26%)
3	0(0%)	17(34%)	17(34%)
4	7(14%)	3(6%)	10(20%)
5	8(16%)	0(0%)	8(16%)
Total	15(30%)	35(70%)	50(100%)

hs-CRP Vs GOS Group:

Out of the 34% cases with GOS score of 4 or 5, i.e those with favourable outcome, 30% had CRP < 10.1 mg/L and 4% had CRP ≥ 10.1 mg/L.

All the remaining 66% cases with GOS score of 1, 2 or 3, (i.e unfavourable outcome) had hs-CRP ≥ 10.1 mg/L.

Table 13: hs-CRP Vs GOS Group

GOS group	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
Favourable	15(30%)	2(4%)	17(34%)
Unfavourable	0(0%)	33(66%)	33(66%)
Total	15(30%)	35(70%)	50(100%)

P= 0.000 SIGNIFICANT

SENSITIVITY/ SPECIFICITY TEST FOR hs-CRP:

Table 14: Sensitivity/ Specificity Test for hs-CRP

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	100%	(89.57, 100)
Specificity	88.24%	(65.66, 96.71)
Positive Predictive Value	94.29%	(81.39, 98.42)
Negative Predictive Value	100%	(79.61, 100)
Diagnostic Accuracy	96%	(86.54, 98.9)

Thus hs-CRP is 100% sensitive and 88.24% specific as a prognostic tool in acute ischemic stroke. hs-CRP has a diagnostic accuracy of 96% in patients with acute ischemic stroke.

DISCUSSION

DISCUSSION

The correlation between hs-CRP levels measured within 48 hours of onset of stroke to that of the functional outcome of the patient at the end of 4 weeks (using GOS) was carried out.

Out of the 50 cases enrolled in the study, 35 cases (70%) had CRP values $\geq$ 10.1 mg/L and 15 cases (30%) had CRP < 10.1 mg/L.

Out of the 35 cases with CRP $\geq$ 10.1 mg/L, 4% had GOS score of 1, 26% cases had GOS score of 2, 34% cases had GOS score of 3.

On the other hand, of the remaining 15 cases with CRP < 10.1 mg/L, none had a GOS score of 1, 2 or 3. 14% cases had a GOS score of 4 and 16% cases had a GOS score of 5.

Out of the 50 patients, 2 died. Both of them had very high hs-CRP levels. Thus patients with CRP levels < 10.1 mg/L had a relatively favourable outcome (GOS score of 1, 2 or 3) when compared to patients with levels $\geq$ 10.1 mg/L (GOS score of 4 and 5).

In our study following statistical analysis were done

1. Mean age of the patients included in this study was 59.90 with SD of 7.360
2. Mean age of female patients was 60.65 with SD 6.852

3. Mean age for male patients was 59.08 with std .deviation of 7.940

4. Out of 26 females enrolled in this study 15 had high Hs-crp level and remaining 9 had normal Hs –crp level.

5. Out of 24 males enrolled in this study 19 had high levels and remaining 5 had normal levels.

6. Mean time of samle collection is 13.96 with SD of 9.95 hrs

7. In this study out of 34 patients who had value 31 people fell in unfavourable group
   P value – highly significant =0.000

8. Out of 29 non smokers 17 had high value and 12 had normal value and out of 21 smokers 17 had high value and 4 had normal value
   P value- 0.095 non significant

9. Out of 29 smokers 13 had favourable GOS score remaining 16 had unfavourable score and out of 21 smokers 5 had favourable score and remaining 16 had unfavourable score
   P value – 0.126 not significant

10. Out of 31 nonalcoholics in this study 19 had high levels of Hs-crp remaining 12 had normal levels and out of 19 alcoholics 15 had high high values remaining 4 had normal value
   P value- 0.194 not significant

11. Out of 31 non alcoholics 14 had favourable GOS score remaining 17 had unfavourable score and out of 19 alcoholics 4 had favourable GOS score and remaining 15 had unfavourable score
   Pvalue – 0.089 non significant

12. Out of 30 persons with high BP 24 had high Hs-crp levels and 6 had normal levels .out of 20 with normal BP 10 had high levels and the remaining 10 had normal levels
   P value - 0.026 significant

13. Out of 30 hypertensives 8 had favourable GOS score and 22 had unfavourable score .out of 20 non hypertensives 10 had favourable score and remaining 10 had unfavourable score
   P value- 0.092 not significant

14. Out of 15 patients with 14 had high levels of Hs-crp remaining one patient had normal level.out of 35 patients with normal serum cholesterol levels 20 had high Hs-crp values remaining 15 had normal values

P value- 0.012 high significant

15. Out of 35 patients who had normal serum cholesterol level 16 patients had favourable score and remaining 19 had unfavourable score. Out of 15 patients who had high serum cholesterol level 2 had favourable score and 13 had unfavourable score

P value- 0.029 significant

16. Out of 40 patients who had normal cardiac status 26 had high Hs-crp levels and 14 had normal level. Out of 10 cardiac patients 8 had high levels and 2 had normal levels

P value -0.363 not significant

17. Out of 40 non- cardiac patients 16 had favourable GOS score and 24 unfavourable score. Out of 10 cardiac patients 2 had favourable score and 8 had unfavourable score

P value- 0.239 not significant

T

his is consistent with the various studies conducted using hs-CRP as a prognostic indicator of acute ischemic stroke.

Table 15: Studies conducted using hs-CRP as a prognostic indicator

S. No	Study	Year
1.	Di Napoli	2001, 2002, 2005
2.	Yusuf Tamam et al	2005
3.	Muir KW, Weir CJ, Alwar W et al	1999
4.	Mitchell S V Elkind et al	2006
5.	Ufuk Emre et al	2007
6.	Winbeck K et al	2002
7.	Kocer A et al	2005
8.	Rost N S et al	2001
9.	Cao J J et al	2003

The correlation of hs-CRP levels with age and gender was studied. There was no statistically significant correlation between age and gender of the patient with the hs-CRP levels. This may be because of the small sample size of our study group. But in a study conducted by So Yeon Ryu et al in 2005, age had an independent association with plasma hs-CRP whereas gender showed no significant association with plasma hs-CRP. Also another study conducted by Rohde Lep et al in 1999 concluded that hs-CRP levels were statistically significant with age, number of cigarettes smoked per day, BP, total cholesterol.

In our study, smoking and alcohol had no statistical significance with hs-CRP levels. This is in contrast to a study conducted by So Yeon Ryu et al in 2005, where smoking had a significant correlation with plasma hs-CRP levels. Smoking is well supposed to give chemical and oxidative stimuli to the cardiovascular system and cause inflammation. The same study also reported that moderate alcohol consumption reduces circulating hs-CRP. Moderate alcohol consumption has anti-inflammatory effects. The mechanism causing moderate alcohol to decrease CRP levels needs further investigation. It involves nuclear factor (NF) – κB (Blanco – Colio et al 2000). NF-κB is a redox sensitive

transcription factor which activates geans involved in the immune, inflammatory or acute phase response, such as cytokines IL – 6 and TNF - α which regulates CRP production by liver. Another study conducted by M. Averina et al in 2003

In our study, total serum cholesterol did not have statistically significant correlation with hs-CRP levels. This is in contrast to a study conducted by So Yeon Ryu et al in 2005. A limitation of our study was that only total serum cholesterol was estimated and not the complete lipid profile.

Our study showed a statistically significant correlation between high BP and hs-CRP. This is consistent with the study conducted by So Yeon Ryu et al in 2005 and Blackburn R et al in 2001.

Diabetes had no statistical significance with hs-CRP in our study. This is in contrast to many of the previous studies. This may be because of the small sample size and also because of the fact that our study included only acute ischemic stroke patients; it was not done exclusively on diabetic subjects.

Table 16: Studies showing significant correlation between hs-CRP levels and DM

S.No	Study	Year
1.	Blackburn R. et al	2001
2.	Minna Soinio et al	2006
3.	So Yeon Ryu et al	2005

Our study also did not show a statistically significant correlation between IHD and hs-CRP levels. This is in contrast to many of the previous studies. This may be because our study included only ischemic stroke patients, it did not include IHD cases without stroke.

Table 17: Studies showing significant correlation between hs-CRP levels and IHD

S.No	Study	Year
1	Liuzzo et al	1994
2	Ferreiros et al	1999
3	winter et al	1999

the major difference between our study and those of other studies mentioned above was that our study involved only hs-CRP levels and not other acute phase reactants like fibrinogens. Also, in our study we assessed the outcome of patients with acute ischemic stroke at the end of four weeks and not at the end of one year. Also, we measured the CRP levels only within 48 after the onset of ischemic stroke and not at the end of four weeks or at the time of discharge. This was because of the cost involved in the measurement of hs-CRP. The other reason, why our study did not have significant correlation with age, sex, DM, IHD was that our study sample size was very small.

The prognostic importance of the 48-hour concentration of CRP may be partly related to the extent of ischemic necrosis and partly to the unknown individual determinants of the intensity of the acute phase reactants. CRP is a very vital indicator of the inflammatory states during the acute phase of an ischemic stroke.

Knowledge of the prognostic influence of the levels of CRP in the outcome of stroke of atherothrombotic etiology helps the clinician to offer realistic expectations to the families of stroke victims.

Thus, CRP can be routinely measured for all stroke patients , as it has been found to provide a statistically significant level of prognostic information as to the eventual outcome of stroke both in short term such as in our study and also over a longterm as was shown in the study by DiNapoli

Also, CRP has a direct relationship with other cardiovascular risk factors, like smoking, alcohol consumption, hypertension, diabetes and cholesterol. Thus CRP levels may be a marker for preclinical cardiovascular disease.

As CRP was found to be an independent risk indicator of further cardiovascular and neurovascular events as shown by the subset of Framingham study, routine CRP screening of susceptible population like chronic smokers and sibilings and first degree relatives of patients with IHD and stroke may prove a valuable indicator for predicting future athreothrombotic events and then it can be assessed as a routine indicator for aspirin prophylaxis.

CONCLUSION

CONCLUSION

- hs-CRP levels showed statistically significant elevation in patients with high blood pressure.
- hs-CRP levels had no significant correlation with age or gender.
- hs-CRP did not show a statistically significant correlation with smoking or cholesterol intake.
- There was no statistically significant correlation between hs-CRP levels and those with diabetes or IHD.

ANNEXURES

PROFORMA

Name: IP No: Serial No:

Age:

Sex:

Occupation:

Address:

Smoking:

Alcohol:

DM:

HT:

IHD:

CLINICAL EXAMINATION:

Pulse rate: BP:

CVS:

RS:

Abdomen:

CNS:

INVESTIGATIONS:

Hb%: Total count:

Differential count P- , L- , E- , M- , B-ESR:

hs-CRP:

Blood urea:

Blood sugar:

Serum creatinine:

Serum electrolytes:

Serum cholesterol:

ECG:

CXR-PA view:

CT brain:

MASTER CHART

	NAME	AGE	SEX	TIME OF SAMPLE COLLECTION (hrs)	GOS SCORE	Hs-CRP LEVEL	Hs-CRP LEVEL	SMOKER	ALCOHOLIC	HYPERTENSION	SERUM CHOLESTEROL	CARDIAC DISEASE
1	MR. GNANAPRAKASH	45	M	6	2	14.5	HIGH	YES	YES	YES	HIGH	YES
2	MR.GUNASEELAN	61	M	14	3	13.8	HIGH	YES	YES	YES	NORMAL	NO
3	MRS.GANDIMATHI	66	F	18	2	10.2	HIGH	NO	NO	NO	NORMAL	NO
4	MR. DAVID	46	M	21	3	11.6	HIGH	YES	YES	YES	NORMAL	YES
5	MRS.INDRAVATHI	62	F	7	3	10.6	HIGH	NO	S.NO	NO	HIGH	NO
6	MRS.MUNNIYAMMAL	67	F	15	2	10.3	HIGH	NO	NO	NO	NORMAL	NO
7	MR.ELUMALAI	53	M	13	5	8.9	NORMAL	NO	NO	NO	NORMAL	NO
8	MR.IDAYATHULLAH	63	M	19	5	9	NORMAL	YES	YES	NO	NORMAL	YES
9	MR.RADHAKRISHNAN	68	M	16	2	12.2	HIGH	YES	YES	YES	HIGH	YES
10	MRS.JAYANTHI	47	F	8	5	9.2	NORMAL	NO	NO	YES	NORMAL	NO
11	MR.JOHNSON	64	M	20	3	13.1	HIGH	YES	YES	YES	NORMAL	NO
12	MRS.DEVI	54	F	21	5	9	NORMAL	NO	NO	NO	NORMAL	NO
13	MR.RAMBAHADUR	69	M	8	1	17.2	HIGH	YES	YES	YES	HIGH	YES
14	MRS.RADHA	48	F	16	3	12.2	HIGH	NO	NO	NO	NORMAL	NO
15	MR.BALASUBRAMANIAN	65	M	17	2	11.2	HIGH	YES	YES	YES	NORMAL	NO
16	MRS.THASIRBANU	70	F	10	5	7.3	NORMAL	NO	NO	YES	NORMAL	NO
17	MR.CHANDRASEKARAN	50	M	7	3	11.3	HIGH	YES	YES	YES	HIGH	NO
18	MRS.GOMATHI	56	F	11	3	13.2	HIGH	NO	NO	NO	NORMAL	NO
19	MRS.JANAKIAMMAL	61	F	13	4	9.7	NORMAL	NO	NO	NO	NORMAL	NO

20	MR.REMIGEORGETHOMAS	66	M	18	3	12.3	HIGH	YES	YES	YES	NORMAL	NO
21	MRS.MANJULA	57	F	11	4	9.2	NORMAL	NO	NO	NO	NORMAL	NO
22	MRS.DEVAKI	62	F	12	2	10	NORMAL	NO	NO	YES	NORMAL	NO
23	MRS.LAKSHMI	67	F	19	5	7	NORMAL	NO	NO	YES	NORMAL	NO
24	MR.SHAHUL HAMEED	52	M	9	3	14.2	HIGH	YES	YES	YES	HIGH	YES
25	MRS.GNANASOUNDARI	63	F	20	3	11.1	HIGH	NO	NO	YES	NORMAL	NO
26	MRS.SULOCHANA	68	F	8	4	10	NORMAL	NO	NO	NO	NORMAL	NO
27	MR.SELVAKUMAR	58	M	21	2	12.7	HIGH	YES	YES	YES	HIGH	NO
28	MRS.SAMPOORNAM	64	F	5	5	12	HIGH	NO	NO	YES	HIGH	NO
29	MRS.VASANTHAMANI	69	F	14	3	10.7	HIGH	NO	NO	NO	NORMAL	NO
30	MRS. MARY	59	F	15	4	10	NORMAL	NO	NO	NO	NORMAL	NO
31	MR.KUMARESAN	65	M	6	2	14.3	HIGH	YES	YES	YES	HIGH	YES
32	MR.SIVASANKARAN	51	M	7	5	10	NORMAL	YES	YES	YES	HIGH	NO
33	MR.SHANMUGAM	60	M	16	3	11.2	HIGH	NO	YES	YES	NORMAL	NO
34	MR.ARAVINDAN	70	M	12	1	16.9	HIGH	YES	YES	YES	HIGH	NO
35	MRS.RAMESWARI	56	F	6	4	10	NORMAL	YES	YES	NO	NORMAL	YES
36	MR.GOVINDARAJALU	57	M	11	2	15.1	HIGH	NO	YES	YES	NORMAL	YES
37	MRS.SUDHA	66	F	5	3	10.3	HIGH	NO	NO	YES	HIGH	NO
38	MR.VENKATESH	58	M	17	4	13	NORMAL	NO	NO	YES	NORMAL	NO
39	MR.MARIAPPAN	67	M	12	2	11.3	HIGH	YES	NO	YES	HIGH	NO
40	MRS.THARA	59	F	7	3	12.3	HIGH	NO	NO	YES	NORMAL	NO
41	MR.SELVAM	46	M	18	4	11.9	HIGH	YES	NO	YES	NORMAL	NO

42	MRS.TAMILMANI	68	F	10	2	13.1	HIGH	NO	NO	YES	HIGH	NO
43	MRS.PRIYASENTHIL	69	F	8	4	11.1	HIGH	NO	NO	YES	NORMAL	NO
44	MR.THIRUNAVUKARASU	60	M	19	3	12.9	HIGH	YES	NO	NO	NORMAL	NO
45	MRS.SHANTHI	55	F	20	3	11.2	HIGH	NO	NO	NO	NORMAL	NO
46	MR.ELANGO	70	M	6	2	12.3	HIGH	YES	NO	YES	HIGH	YES
47	MRS.PRIYADARSHINI	47	F	21	4	9	NORMAL	NO	NO	NO	NORMAL	NO
48	MRS.SANGEETHAMAL	58	F	14	3	10.3	HIGH	NO	NO	NO	NORMAL	NO
49	MR.RAMAHATHULLAH	54	M	15	4	7.9	NORMAL	YES	YES	NO	NORMAL	NO
50	MRS.MALRVIZHI	59	F	16	2	11.1	HIGH	NO	NO	NO	NORMAL	NO

ABBREVIATIONS

%	-	Percentage
APP	-	Acute phase protein
BP	-	Blood pressure
CAHD	-	Coronary artery heart disease
CHD	-	Coronary heart disease
CI	-	Confidence Interval
CRP-US	-	C-Reactive Protein ultra sensitive
DM	-	Diabetes mellitus
Gp	-	Group
hs-CRP	-	High sensitivity C-Reactive Protein
HT	-	Hypertension
IHD	-	Ischemic heart disease
IL	-	Interleukin
JNC	-	Joint National Committee
mg/L	-	Milligram/litre
MI	-	Myocardial infarction
m-RNA	-	Messenger – RNA
OCP	-	Oral contraceptive pill
SAA	-	Serum amyloid A
SAH	-	Subarachnoid haemorrhage
SD	-	Standard deviation
TIA	-	Transient ischemic attack
yrs	-	Years

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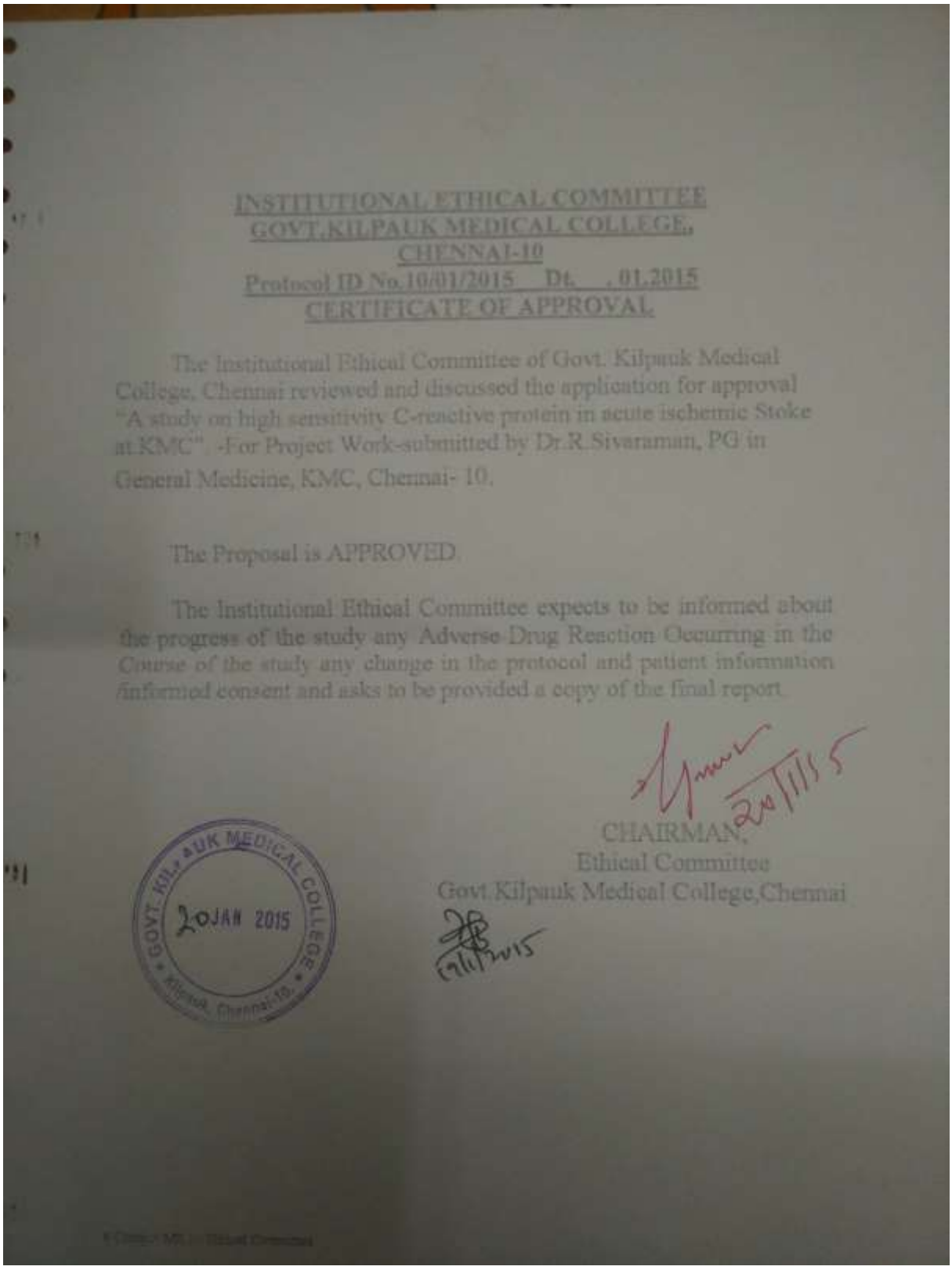

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID No.10/01/2015 Dt. .01.2015
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A study on high sensitivity C-reactive protein in acute ischemic Stoke at KMC". -For Project Work-submitted by Dr.R.Sivaraman, PG in General Medicine, KMC, Chennai- 10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

20/1/15

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

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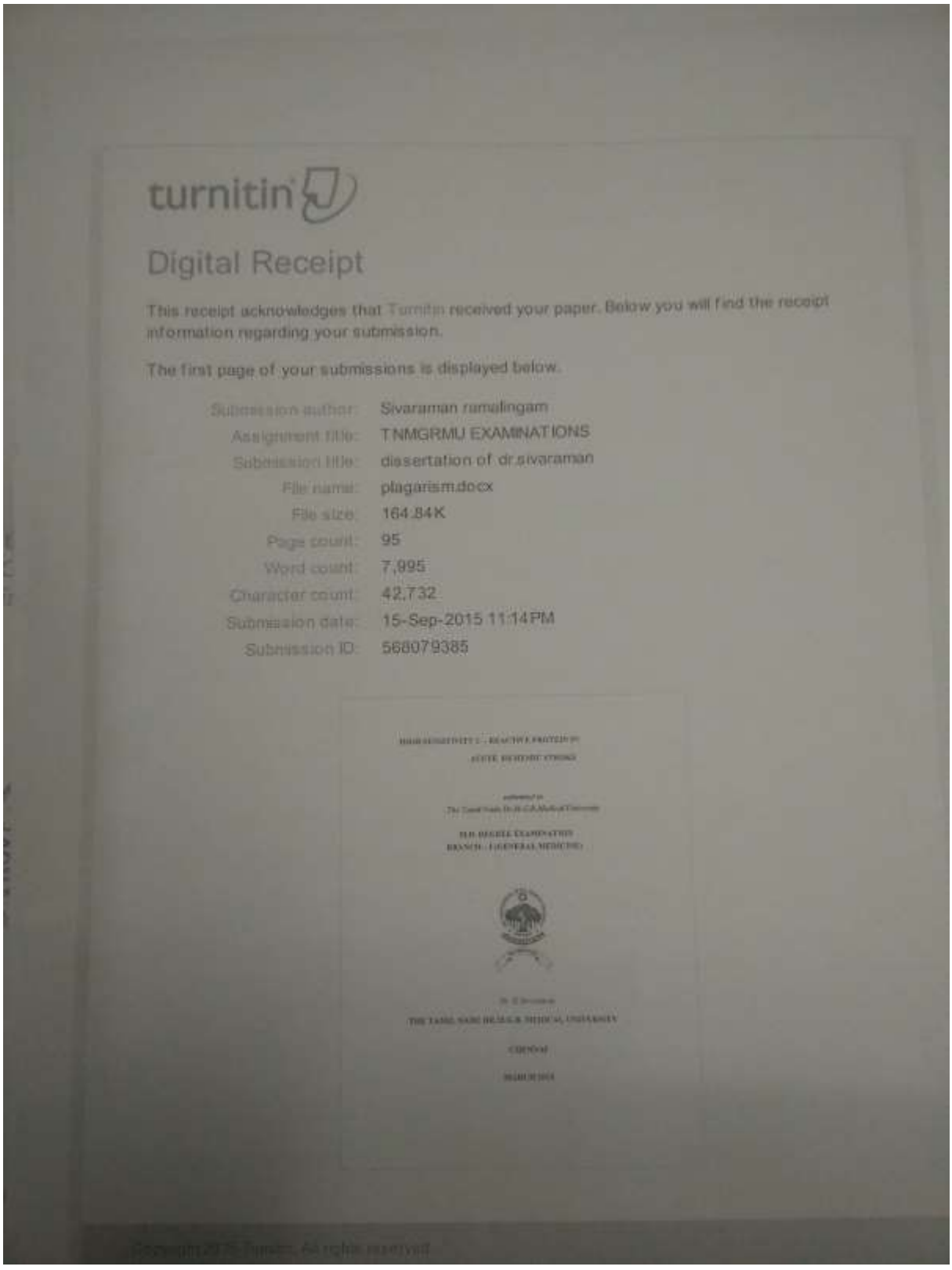

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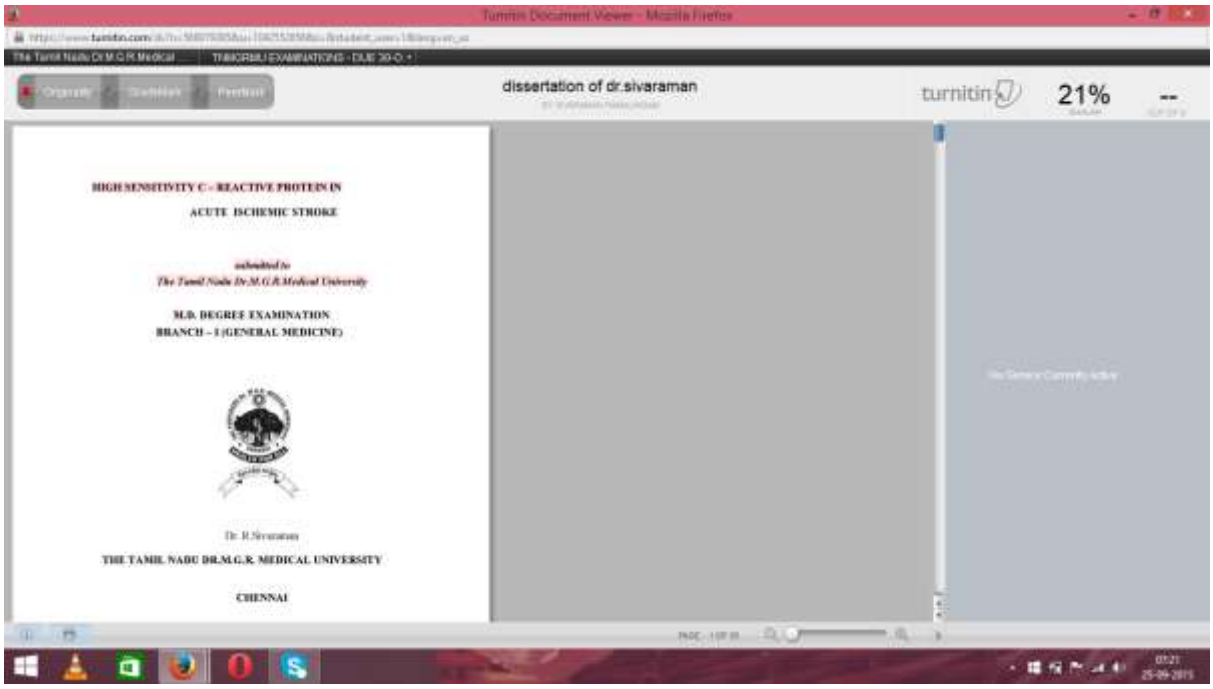
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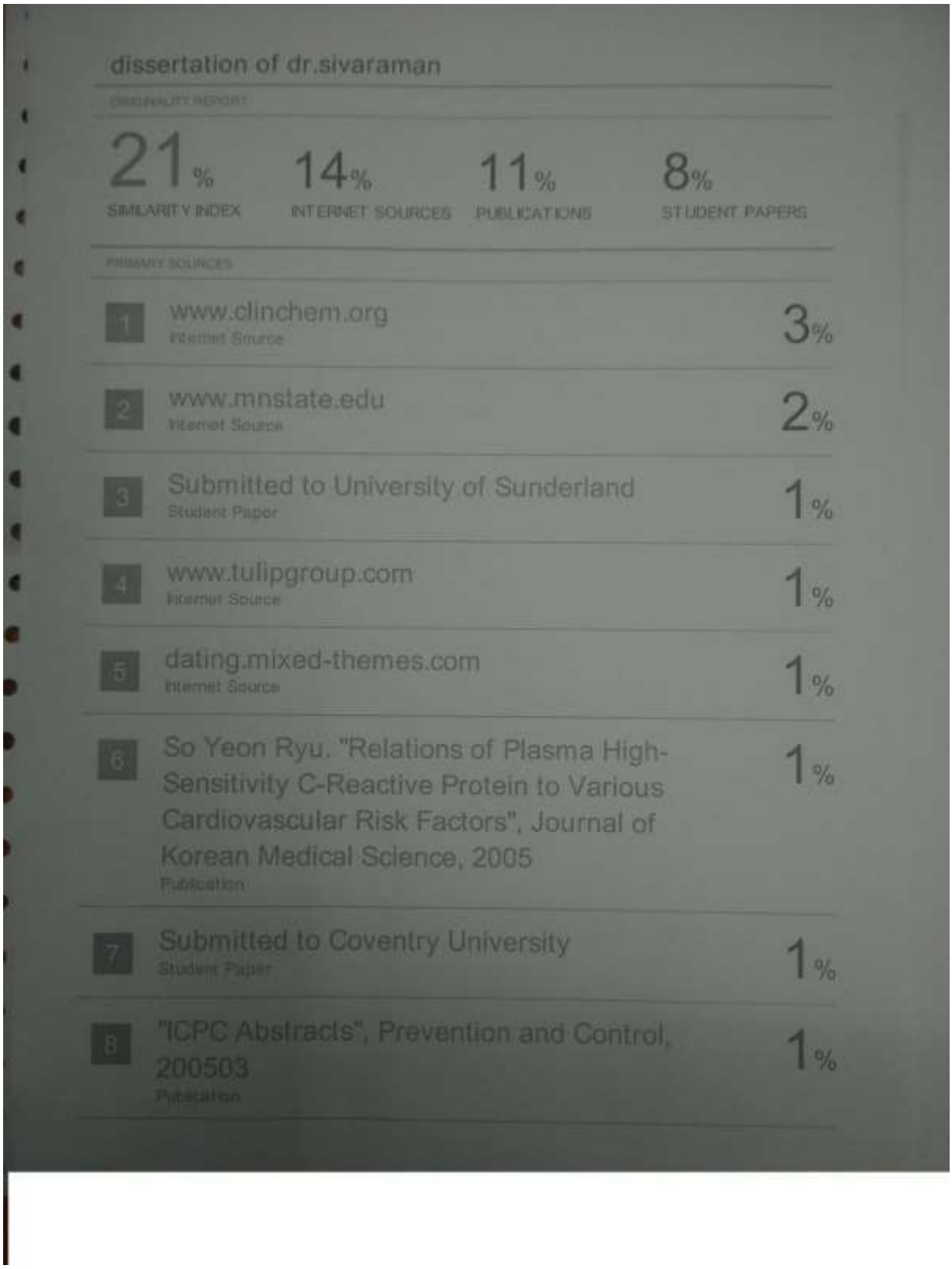

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